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ORIGINAL ARTICLE

Efficacy of bath-psoralen and ultraviolet A therapy for mycosis fungoides – retrospective analysis of 62 cases

Yoichi Shintani[1] | Emi Nishida[1] | Takuya Furuhashi[1] | Shinnosuke Muramatsu[1] | Ryoji Kubo[1] | Motoki Nakamura[1] | Shoichi Watanabe[1] | Hideyuki Masuda[1] | Kyoko Ikumi[1] | Kazuhiko Matsumoto[1] | Sayuri Yamazaki[2] | Akimichi Morita[1]

[1]Department of Geriatric and Environmental Dermatology, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan

[2]Department of Immunology, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan

Correspondence
Akimichi Morita, M.D., Ph.D., Department of Geriatric and Environmental Dermatology, Nagoya City University Graduate School of Medical Sciences, 1-Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya 467-8601, Japan.
Email: amorita@med.nagoya-cu.ac.jp

Abstract

Photochemotherapy with psoralen and ultraviolet A (PUVA) is widely used for refractory skin diseases. Bathwater delivery of 8-methoxypsoralen (8-MOPS) with subsequent UVA irradiation (bath-PUVA) or oral administration of 8-MOPS with UVA is used to treat mycosis fungoides. We retrospectively analyzed 62 patients with mycosis fungoides (8 stage IA, 30 stage IB, 5 stage IIB, 18 stage IIIA, and 1 stage IVA2) treated with bath-PUVA at the Dermatology Clinic of Nagoya City University Hospital from November 2004 to December 2013. A complete response was achieved in 37 (59.7%) patients, a partial response was achieved in 16 (25.8%), and stable disease was achieved in 6 (9.7%). Progressive disease was observed in 3 (4.8%) patients. Almost all patients in stage IA/IB achieved a complete response. Of the 5 stage IIB patients, 2 achieved a partial response, 1 achieved stable disease, and 2 had progressive disease. The serum concentrations of soluble interleukin-2 receptor and lactate dehydrogenase decreased significantly following treatment with bath-PUVA ($p < 0.001$). We examined the risk factors of patients whose stage progressed despite PUVA treatment. A multivariate Cox regression analysis of risk factors associated with stage progression yielded a hazard ratio of 28.5 for stage IIb. Treatment with bath-PUVA is highly effective in the early stages of mycosis fungoides, and partially effective in advanced stages.

KEYWORDS
mycosis fungoides, photochemotherapy, retrospective studies, skin disease, ultraviolet therapy

1 | INTRODUCTION

Mycosis fungoides (MF) is the most common cutaneous lymphoma observed during dermatologic medical examinations. MF is considered a low-grade lymphoma because the premycotic and mycotic phases can last for several years. Owing to the relatively low awareness of the disease, many patients seek dermatologic consultation for the first time after their condition has already progressed to the mycotic or tumorous phases. This condition can lead to death within a few months following tumor formation, ulceration, leukemic transformation, and visceral invasion. Proactive treatment during the premycotic and mycotic phases may prevent stage progression, thereby improving both the survival rate and prognosis.

Abbreviations: LDH, lactate dehydrogenase; MF, mycosis fungoides; PD, progressive disease PUVA, psoralen and ultraviolet A; SD, stable disease sIL-2R, soluble interleukin-2 receptor; 8-MOPS, 8-methoxypsoralen.

Phototherapy is highly effective for early-stage MF, and phototherapy guidelines for patients with MF and Sezary syndrome in the United States were reported.[1] The 2020 Clinical Practice Guidelines for Cutaneous Lymphoma by the Japanese Dermatological Association recommend topical steroid therapy, phototherapy [broadband-Ultraviolet B (UVB), narrowband Ultraviolet B (UVB), or Psoralen and ultraviolet A (PUVA)], or local radiation therapy during the early stage.[2] In our clinic, we have used bath-PUVA therapy to treat MF since 1998. Here, we report the efficacy of this treatment in 62 patients for whom data were available for the study.

2 | METHODS

2.1 | Study method

This was a single-center, retrospective cohort study of patients with MF treated with bath-PUVA. Patients diagnosed with MF who were admitted to the Nagoya City University Hospital and underwent bath-PUVA therapy during a 10-year period from November 2004 to December 2013 were retrospectively reviewed. This study was performed in accordance with protocols approved by the Ethics Review Board of Nagoya City University, the Declaration of Helsinki, and the Ethical Guidelines for Clinical Research.

2.2 | MF staging

The stages of patients treated in 2011 and earlier were re-evaluated according to the tumor–node–metastasis-blood classification reported in 2011 by the International Society for Cutaneous Lymphomas and Cutaneous Lymphoma Task Force of the European Organization of Research and Treatment of Cancer.[3]

2.3 | Irradiation protocol for bath-PUVA therapy

Patients soaked in 0.0001% 8-methoxypsoralen (8-MOPS) bathwater (37°C) for 15 min and underwent subsequent UVA treatment five times a week. The UV dose increment schedule was as follows: 0.2, 0.5, 0.8, 1.1, 1.5, 1.9, 2.3, 2.8, 3.3, 4.0 J/cm^2; the dose was maintained at 4.0 J/cm^2 thereafter until May 2005. Beginning in June 2005, the initial UV dose was set at 0.5 J/cm^2 and increased to 4.0 J/cm^2 in 0.5-J/cm^2 increments; thereafter, the dose was maintained at 4.0 J/cm^2. Patients were discharged when the lesions disappeared and then re-admitted for five weekly irradiation treatments when lesions recurred. Some patients from 2006 or earlier received combination therapy with interferon-gamma.

2.4 | Assessment of efficacy

The response was defined as follows:[3] complete response (CR), 100% clearance of skin lesions; partial response (PR), 50%–99% clearance of skin disease from baseline without new tumors (T3) in patients with T1-, T2-, or T4-only skin disease; stable disease (SD), <25% increase to <50% clearance in skin disease from baseline without new tumors (T3) in patients with T1-, T2-, or T4-only skin disease; progressive disease (PD), 25% increase in skin disease from baseline or new tumors (T3) in patients with T1-, T2-, or T4-only skin disease; and loss of response, a skin score increase greater than the sum of the nadir plus 50% of the baseline score in patients with a CR or PR.

2.5 | Statistical analysis

Statistical analysis was performed using Excel (Microsoft Corp., Redmond, WA, USA), Pharmaco Analyst (Scientist Press Co. Ltd., Tokyo, Japan), and R version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria). A paired Student's t-test was used to compare blood chemistries before and after bath-PUVA therapy. Overall survival and disease-specific survival were estimated by the Kaplan–Meier method. The length of time was defined from the start of bath-PUVA therapy. Deaths caused by MF were treated as an endpoint for disease-specific survival. Overall survival was the actual survival period. We examined the risk factors of patients whose stage progressed despite PUVA treatment. Univariate and multivariate Cox regression analyses were performed (R version 3.6.3 using the survival package). All reported *p*-values are 2-tailed, with a value <0.05 considered significant.

3 | RESULTS

3.1 | Patient characteristics

A total of 62 patients were retrospectively enrolled in the study: 40 men (65%) and 22 women (35%). Mean (standard deviation) age at onset of MF was 62.7 (17.7) years (median age, 66 years; range, 13–94 years). Stage at the initial consultation was as follows: IA (n = 8); IB (n = 30); IIB (n = 5); IIIA (n = 18); and IVA2 (n = 1). Mean number of hospital admissions for PUVA treatment: two for patients in stage IA; three for patients in stages IB, IIB, and IIIA; and one for patients in stage IVA2 (Figure 1a–d).

3.2 | Treatment response

3.2.1 | Skin symptoms

Among patients with stage IA MF, 100% achieved a CR, and among patients in stage IB, 70% achieved a CR and 93% achieved a partial response (PR) or better. Among patients in stage IIB, 40% achieved a PR, 20% achieved stable disease (SD), and 40% had progressive disease (PD), indicating that many of these patients had an insufficient response. In contrast, patients in stage IIIA exhibited a greater response, with a 44% CR and 39% PR (Figure 2).

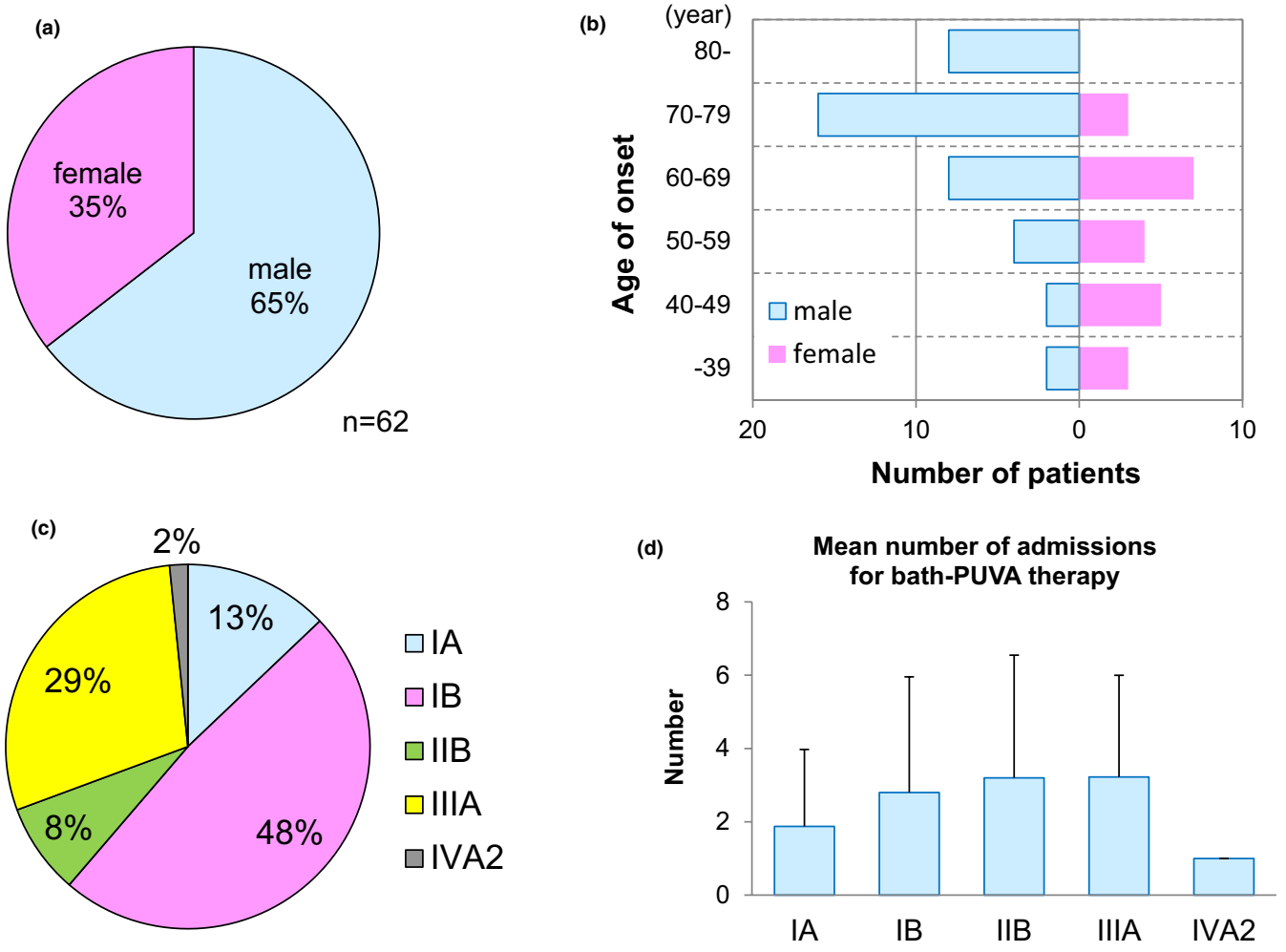

FIGURE 1 Patient characteristics. (a) Subjects were 40 men (65%) and 22 women (35%). (b) Mean age at onset was 62.7 years with a median age of 66 years. Men were significantly older at the time of onset. The sex difference in the age at onset was significant ($p = 0.0029$). (c) The most common stage at diagnosis was IB (48%). (d) Mean number of bath- psoralen and ultraviolet A (PUVA) therapy cycles (1 cycle = patient receives irradiation on consecutive days while hospitalized and is subsequently discharged) was 1.9 cycles (stage IA), 2.8 cycles (stage IB), 3.2 cycles (stage IIB), and 3.2 cycles (stage IIIA). Thus, patients in stage IA underwent fewer treatment cycles

3.2.2 | Blood results

Comparisons before and after treatment stratified by stage revealed a significant decrease in the serum concentrations of both lactate dehydrogenase (LDH) and soluble interleukin-2 receptor (sIL-2R) in patients in stages IB and IIIA. In contrast, no significant differences in the serum concentrations of either LDH or sIL-2R were observed between before and after treatment in patients in stages IA and IIB (Figure 3).

3.3 | Recurrence

In some patients with MF, bath-PUVA therapy prevents recurrence of the rash after only one course of treatment. To investigate such circumstances, remission was defined as the absence of recurrence for at least 1 year after one inpatient treatment among patients who exhibited a CR to bath-PUVA therapy with lesion disappearance, and the percentages of patients who achieved remission at each stage were evaluated. Remission was achieved in approximately 57.1% of patients in stage IA and 26.1% of patients in stage IB. Remission was also achieved in 7.1% of patients in stage IIIA (Figure 4). For patients in stage IA and IB (the most frequent stages in this study), the number of bath-PUVA sessions administered during one inpatient treatment was compared between those who achieved remission and those with repeated recurrence; no significant differences were detected (data not shown). Comparison of the blood data between those who achieved remission and those with repeated recurrence revealed no significant differences in the pre-treatment serum LDH or sIL-2R, or in the rate of decrease from pre- to post-treatment for either factor (data not shown).

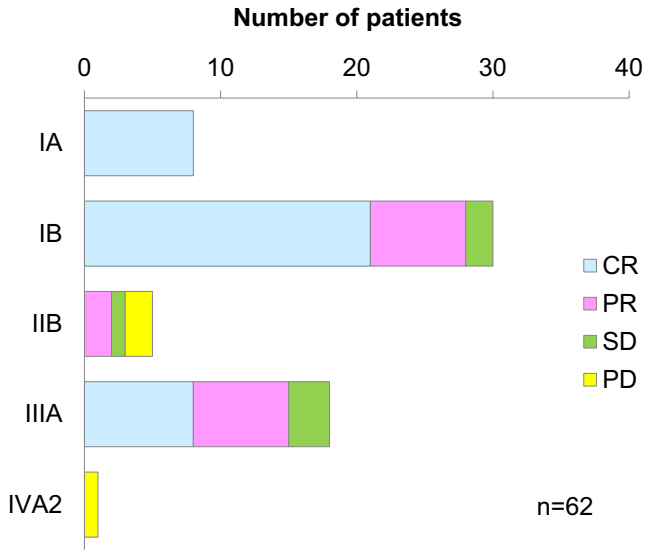

FIGURE 2 Bath- psoralen and ultraviolet A (PUVA) therapy responses among the stages. One patient experienced repeated recurrence and underwent multiple inpatient treatments. This graph shows treatment responses by patient

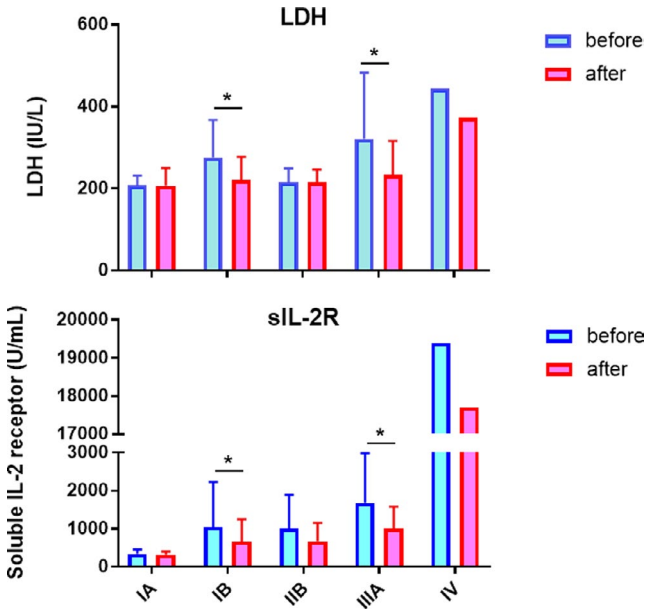

FIGURE 3 Comparison of serum lactate dehydrogenase (LDH) and soluble interleukin-2 receptor (sIL-2R) before and after bath-psoralen and ultraviolet A (PUVA) therapy by stage. Serum concentrations of both LDH and sIL-2R significantly decreased in stages IB and IIIA, but no significant differences were detected in stages IA and IIB. The data are presented as mean ± standard error. *$p < 0.05$ (paired t-test)

3.4 | Unmanaged cases

In six patients, the pathologic condition could not be managed with bath-PUVA therapy. Patient 1 was initially diagnosed with stage IB MF and experienced temporary symptom relief after starting bath-PUVA therapy. Tumor lesions on the head appeared 7 years later. The patient subsequently underwent tomotherapy (24 Gy) and continues to receive outpatient care 5 years later. Patient 2 presented with stage IIB MF and multiple tumor lesions. The patient underwent chemotherapy, but ultimately died. Patient 3, diagnosed with stage IIB MF, initially presented primarily with plaques and underwent bath-PUVA therapy. The plaques gradually spread over a larger area, and both the size and number of tumor lesions subsequently increased. Despite undergoing tomotherapy, the patient died. Patient 4 exhibited rapid-onset MF over the course of a few months and sought medical consultation after the appearance of a tumor. Leukemic transformation occurred shortly thereafter and the patient died. Patient 5 presented with stage IIIA erythroderma and developed multiple tumor lesions after medical consultation. The patient underwent various types of chemotherapy, but ultimately died. Patient 6 was diagnosed with atopic dermatitis from childhood and had undergone treatment at a local hospital. The patient consulted our department after lesion exacerbation and the development of a low-grade fever. The patient was diagnosed with stage IVA2 MF and initially underwent bath-PUVA. Because bath-PUVA resulted in no improvement, the patient received an allogeneic bone marrow stem cell transplantation and subsequently achieved remission.

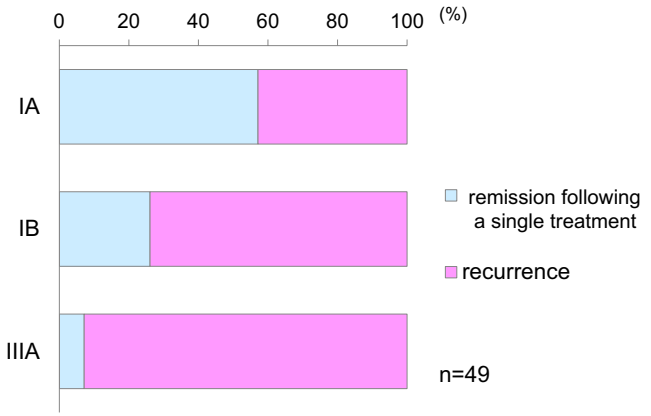

FIGURE 4 Recurrence rate in patients with a complete response (CR) to bath-psoralen and ultraviolet A (PUVA). In some patients with mycosis fungoides (MF), bath-PUVA therapy prevents recurrence of the rash after only one treatment cycle, and such circumstances were investigated. Remission was defined as the absence of recurrence for at least 1 year after one cycle of inpatient treatment among patients who had a CR to bath-PUVA therapy and whose rash disappeared, and the percentages of patients in each stage who achieved remission were evaluated. Remission was achieved in approximately 57.1% of patients in stage IA and 22.2% of patients in stage IB. Remission was also achieved in 7.1% of patients in stage IIIA

3.5 | Survival analysis

The 5-year overall survival from the day of diagnosis measured using the Kaplan–Meier method was 100% for patients in stage IA, 85%

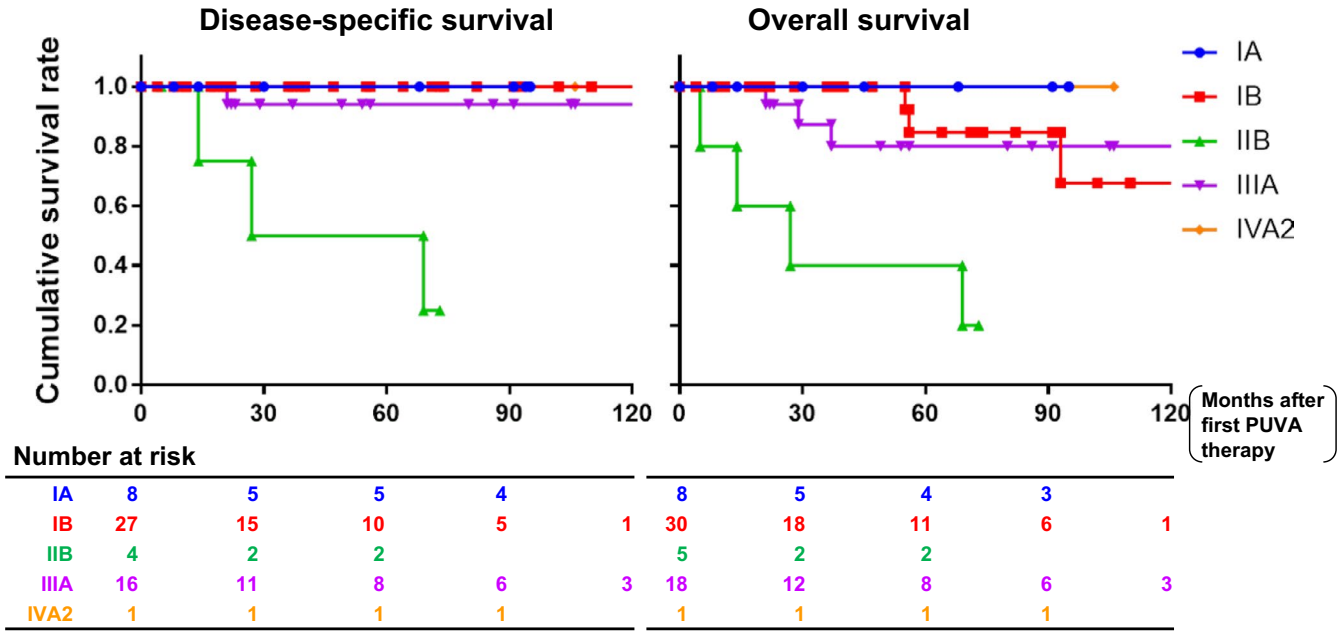

FIGURE 5 Survival according to the stage (Kaplan–Meier method). The 5-year disease-specific survival rate was 100% for patients in stage IA, 100% for patients in stage IB, and 94% for patients in stage IIIA, but 50% for patients in stage IIB. The 5-year overall survival rate was 100% for patients in stage IA, 85% for patients in stage IB, 80% for patients in stage IIIA, and 40% for patients in stage IIB

for patients in stage IB, 40% for patients in stage IIB, and 80% for patients in stage IIIA. The 5-year disease-specific survival for death due to primary disease alone was 100% for patients in stage IA, 100% for patients in stage IB, 50% for patients in stage IIB, and 94% for patients in stage IIIA (Figure 5).

3.6 | Factors related to stage progression

The 5-year stage progression-free rate was 100% for patients in stage IA, 94% for patients in stage IB, 94% for patients in stage IIIA, and 53% for patients in stage IIB (Figure 6). We examined the risk factors of patients who progressed in stage despite PUVA treatment. A multivariate Cox regression analysis of risk factors associated with stage progression yielded a hazard ratio of 28.5 for stage IIb. No other factors were found to have a significant effect, e.g., age, sex, LDH and sIL-2R levels before PUVA treatment (Table 1).

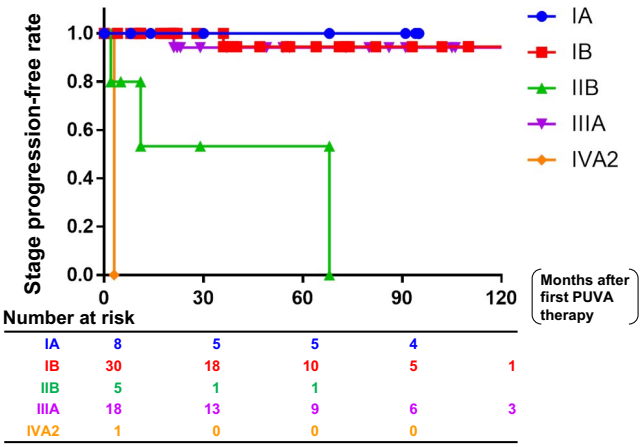

FIGURE 6 Stage progression according to the stage (Kaplan–Meier method). Stage progression according to the stage showed that the 5-year stage progression-free rate was 100% for patients in stage IA, 94% for patients in stage IB, 94% for patients in stage IIIA, and 53% for patients in stage IIB

3.7 | Safety

None of the patients exhibited any severe (grade 3 or more) adverse events during bath-PUVA therapy.

4 | DISCUSSION

In the present study, we investigated patients with MF who underwent bath-PUVA therapy at our hospital after 1998. The male-to-female ratio was 13:7, consistent with previous reports that this condition is more common in men. Men were also significantly older at the time of onset. Bath-PUVA therapy was extremely effective for patients in stages IA and IB, with a CR of 100% and 70%, respectively. Many patients in stage IIB, however, exhibited an insufficient response (PR 40%, SD 20%, and PD 40%). In contrast, favorable responses were observed in patients in stage IIIA, with a CR of 44% and a PR of 39%. Bath-PUVA therapy facilitates percutaneous penetration of psoralen into the lesions and also allows for a

TABLE 1 Univariate and multivariate Cox regression analysis for stage progression

	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p*	HR	95% CI	*p*
Sex						
Male	1.000 (Ref.)	–	–	1.000 (Ref.)		
Female	0.920	0.151–5.600	0.928	0.889	0.126–6.265	0.906
Age (per 10 years)	0.933	0.529–1.646	0.811	0.913	0.383–2.174	0.837
Stage						
Ia + Ib	1.000 (Ref.)	–	–	1.000 (Ref.)	–	–
IIb	29.740	3.061–289.040	0.003	28.480	2.514–322.600	0.007
III	1.848	0.115–29.585	0.664	2.657	0.131–53.940	0.525
LDH (per 10 IU/L)	0.932	0.807–1.076	0.336	0.983	0.811–1.191	0.861
sIL-2r (per 100 U/mL)	0.959	0.864–1.065	0.435	0.968	0.808–1.160	0.725

Abbreviations: CI, confidence interval; HR, hazard ratio; LDH, lactate dehydrogenase; sIL-2r, soluble interleukin-2 receptor.

greater amount of UVA irradiation. For stage IIB lesions with tumor formation, however, poor psoralen and UVA penetration might be expected. In contrast, although the lesions were spread over a wider area in patients in stage IIIA, the individual lesions exhibited tumor cell invasion that localized from the epidermis to the upper dermis, which is considered to contribute to the greater treatment response observed in patients in stage IIIA.

Among patients whose rash disappeared at least once (n = 49), remission was achieved after one treatment cycle in 57% of patients in stage IA and 26.1% of patients in stage IB. Of these patients, the number of UV irradiation sessions during one inpatient treatment course was not significantly different between those who achieved remission and those who experienced a recurrence. These results indicated that although stage progression can be suppressed by administering bath-PUVA therapy at an early stage of the disease. The results of the present study support previous findings that long-lasting disease-free intervals are possible after only one course of PUVA in early-stage MF.[1]

The blood data revealed significant overall improvements in the serum LDH and sIL-2R when compared before and after bath-PUVA therapy. These results corroborate the reduction in the number of tumor cells in the lesions after bath-PUVA therapy. Examination by stage revealed significant reductions in both serum LDH and sIL-2R for patients in stages IB and IIIA. No significant differences were observed, however, in patients in stages IA and IIB. These findings may be due to the lower number of tumor cells and normal concentrations (mean) of pre-treatment serum LDH and sIL-2R in patients with stage IA MF, and also the lower treatment response against tumors in patients with stage IIB MF. Analysis of survival (measured value) after starting bath-PUVA therapy showed a 5-year overall survival of 100% for patients in stage IA, 85% for patients in stage IB, 80% for patients in stage IIIA, and 40% for patients in stage IIB. A multivariate Cox regression analysis of risk factors associated with stage progression yielded a hazard ratio of 28.5 for stage IIb.

The mechanism of PUVA therapy is considered to be UV-induced T cell apoptosis.[4–7] PUVA therapy also reduces the number of infiltrating CCR4-positive cells and regulatory T cells.[8]

The present study revealed favorable effects of bath-PUVA therapy against MF when administered during an early stage before tumor formation. A large number of patients were included in this retrospective analysis of bath-PUVA therapy. Similar effects of bath-PUVA therapy were observed in 16 patients with early-stage (IA and IB) MF.[9] Patients with early-stage MF who were refractory to narrowband UVB were also treated and exhibited a 50% CR and a 33% PR.[10] Our results indicate that administering bath-PUVA therapy at an early stage is an effective therapeutic approach for patients with MF.

CONFLICT OF INTEREST

None declared.

ORCID

Emi Nishida https://orcid.org/0000-0001-6563-1274
Takuya Furuhashi https://orcid.org/0000-0002-2476-0675
Motoki Nakamura https://orcid.org/0000-0003-4431-7782
Kyoko Ikumi https://orcid.org/0000-0003-1401-0966
Akimichi Morita https://orcid.org/0000-0001-8372-3754

REFERENCES

1. Olsen EA, Hodak E, Anderson T, Carter JB, Henderson M, Cooper K, et al. Guidelines for phototherapy of mycosis fungoides and Sézary syndrome: a consensus statement of the United States Cutaneous Lymphoma Consortium. *J Am Acad Dermatol*. 2016;74:27–58.
2. Ohtsuka M, Hamada T, Miyagaki T, Shimauchi T, Yonekura K, Kiyohara E, et al. Outlines of the Japanese guidelines for the management of primary cutaneous lymphomas 2020. *J Dermatol*. 2021;48:e49–71.
3. Olsen EA, Whittaker S, Kim YH, Duvic M, Prince HM, Lessin SR, et al. Clinical end points and response criteria in mycosis fungoides and Sézary syndrome: a consensus statement of the international society for cutaneous lymphomas, the United States cutaneous lymphoma consortium, and the cutaneous lymphoma task force of the European organisation for research and treatment of cancer. *J Clin Oncol*. 2011;29:2598–607.

4. Morita A. Photodermatology-therapeutic photomedicine for skin diseases. In: Kabashima K, editor. *Immunology of the skin*. Tokyo: Springer Japan; 2016. p. 477–88.
5. Krutmann J, Morita A, Chung JH. Sun exposure: what molecular photodermatology tells us about its good and bad sides. *J Invest Dermatol*. 2012;132:976–84.
6. Krueger JG, Wolfe JT, Nabeya RT, Vallat VP, Gilleaudeau P, Heftler NS, et al. Successful ultraviolet B treatment of psoriasis is accompanied by a reversal of keratinocyte pathology and by selective depletion of intraepidermal T cells. *J Exp Med*. 1995;182:2057–68.
7. Morita A. Current developments in phototherapy for psoriasis. *J Dermatol*. 2018;45:287–92.
8. Kato H, Saito C, Ito E, Furuhashi T, Nishida E, Ishida T, et al. Bath-PUVA therapy decreases infiltrating CCR4-expressing tumor cells and regulatory T cells in patients with mycosis fungoides. *Clin Lymphoma Myeloma Leuk*. 2013;13:273–80.
9. Weber F, Schmuth M, Sepp N, Fritsch P. Bath-water PUVA therapy with 8-methoxypsoralen in mycosis fungoides. *Acta Derm Venereol*. 2005;85:329–32.
10. Pavlotsky F, Hodak E, Ben Amitay D, Barzilai A. Role of bath psoralen plus ultraviolet A in early-stage mycosis fungoides. *J Am Acad Dermatol*. 2014;71:536–41.

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