

CLINICAL REPORT

Bath-water PUVA Therapy with 8-Methoxypsoralen in Mycosis Fungoides

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PUVA therapy is widely used for early stage mycosis fungoides. While the efficacy of PUVA with oral 8-methoxypsoralen (8-MOP) is well documented, the use of its topical variation, bath-water PUVA therapy with 8-MOP has not been studied. The purpose of this study was to assess the effect of 8-MOP bath-water PUVA therapy in adult patients with early stage mycosis fungoides. We retrospectively evaluated the outcomes of bath-water delivery of 8-MOP (1 mg l^{-1}) in 16 patients with early stage mycosis fungoides. In all patients complete response was achieved after a mean duration of 63 days requiring 29 treatments and a mean cumulative UVA dose of 33 J cm^{-2} . The time to relapse after complete clinical clearance was $45.6 (\pm 9.2)$ weeks. In comparison, oral PUVA therapy with 8-MOP resulted in complete response after 64.5 days (25.8 treatments) with a mean relapse-free period of $30 (\pm 3.5)$ weeks. We conclude that bath-water PUVA therapy with 8-MOP is a valuable phototherapeutic alternative, which should be considered for patients in whom systemic psoralen cannot be used.
Key words: mycosis fungoides; lymphoma; PUVA; skin.

(Accepted January 10, 2005.)

Acta Derm Venereol 2005; 85: 329–332.

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Standard treatment of early stage mycosis fungoides (MF) includes topical corticosteroids, psoralen+ultraviolet (UVA) (PUVA), UVB, topical chemotherapy, i.e. mechlorethamine (nitrogen mustard) or carmustin (BCNU), and total skin electron beam radiation therapy (1, 2). Treatment of MF with PUVA was first reported by Gilchrist et al. (3) in 1976 and Konrad et al. (4) in 1978. Since then, many studies have confirmed the efficacy of this treatment modality (5–10), which today is the therapeutic mainstay in early MF.

Bath-water PUVA (balneophotochemotherapy) has been developed as a topical modification of oral PUVA therapy (11). Bath-water PUVA with 8-MOP has been shown to be beneficial for many skin disorders: psoriasis (12), granuloma anulare (13), atopic dermatitis (14), lichen planus (15), lichen sclerosus et atrophicus (16), localized scleroderma (17), chronic palmoplantar eczema (18, 19) and lymphomatoid papulosis (20). Comparative studies in

psoriasis showed that bath-water PUVA is as effective as oral PUVA but requires less cumulative UVA (12, 21, 22). To the best of our knowledge, there is only a single report on bath-water PUVA in MF in which trimethylpsoralen (TMP) was used instead of 8-MOP (23). The main advantage of bath-water PUVA therapy over oral PUVA therapy is the avoidance of relevant systemic absorption, thus diminishing the risk of systemic side effects. Cataract development is a problem in oral, but not in topical PUVA therapy. Nausea is a frequent and sometimes limiting side effect of oral 8-MOP. Some patients fail to respond to oral PUVA therapy because of poor psoralen absorption. Furthermore, oral PUVA therapy is less suitable for patients taking multiple drugs because of the risk of overloading liver metabolism. Strict compliance is needed for oral PUVA therapy in taking oral 8-MOP exactly 1 hour before irradiation and avoiding sunlight exposure on treatment days. In contrast, bath-water PUVA therapy lacks these systemic side effects of psoralen, requires less cumulative UVA irradiation and involves less post-treatment photosensitivity. Disadvantages of bath-water PUVA are higher therapy costs and the need for bathing units at, or close to, the phototherapy unit.

In view of its advantages over oral photochemotherapy, all patients with early MF received bath-water PUVA therapy in our department from 1995 onwards except those who preferred oral treatment for personal or medical reasons (e.g. cardiac disease). In this report, we retrospectively evaluate the results of this treatment regimen in 16 patients.

PATIENTS AND METHODS

Patients

Sixteen patients (11 men, 5 women) treated with bath-water PUVA were evaluable between 1995 and 2003. The patients' mean age at the time of treatment was $53.2 (\pm 3.9; 21-73)$ years. Six patients were classified as skin type II, 10 patients as skin type III (according to Fitzpatrick) (24). Fourteen patients had never received any phototherapy before initiation of bath-water PUVA. Two patients had received oral PUVA before (one patient had received 11 courses, the other 5 courses).

All patients included in this study had MF stage Ia or Ib by clinical and histological criteria (25, 26); limited or generalized patches and plaques without lymph node or visceral organ involvement and circulating Sézary cells. For classification and staging, all patients underwent physical examination, complete

blood cell count, investigation of blood chemistry, CD4/CD8 ratio, neopterin, serum interleukin-2 receptor, chest X-ray and abdominal and lymph node ultrasound. Patients with head and/or neck involvement were not included. During treatment the patients did not use any other systemic or topical treatment except emollients.

Bath-water PUVA therapy

Thirty ml of a 0.5% alcoholic solution of 8-MOP (5 g 8-MOP in 1000 ml of 96% ethanol) (Gerot Pharmazeutika, Vienna) were added to 150 litres of bath water (37°C), resulting in a final concentration of 1 mg l⁻¹ 8-MOP. Patients stayed in the bath for 20 min and were advised to wipe the skin dry immediately before UVA irradiation. Whole body UVA was given in a Waldmann 7001 PUVA cabinet equipped with 40 UVA fluorescent tubes (Waldmann F85/100W PUVA tubes). The irradiance of the tubes was 10–18 mW cm⁻² UVA during the study period.

Treatment regimen

Treatment was started at 0.3 J cm⁻² UVA, and UVA doses were increased by 0.3 J cm⁻² every fourth treatment up to a maximum of 1.5–2.7 J cm⁻² depending on the patient's tolerance. In case of mild to moderate phototoxicity, treatment was interrupted for a few days up to 1 week, and the UVA dose was adapted to the patient's tolerance.

All patients were treated four times weekly until complete clinical clearance was achieved, followed by 2–4 weeks of maintenance therapy (two to three times weekly at the maximum dose). By definition, complete clearance was achieved when all signs of erythema, scaling or skin atrophy were resolved at all sites.

After completing a therapy cycle (i.e. initial plus maintenance treatment), the patients entered an open-ended follow-up period in which clinical skin and lymph node evaluation as well as laboratory controls (blood cell count, blood chemistry, CD4/CD8 ratio, serum neopterin, serum interleukin-2 receptor) were performed every 3 months. The mean total follow-up period was 41.2 (±5.5; 4–78) months.

When relapses became manifest, bath-water PUVA treatment was considered and applied again in five patients according to the same protocol as above. Four of 16 patients received one and 1 patient received 2 additional bath-water PUVA therapy cycles. Other patients with relapse were treated with topical steroids, treated elsewhere with oral PUVA or UVB or refused further therapy.

RESULTS

Bath-water PUVA with 8-MOP resulted in complete clearance of MF patches in all of the 16 patients (Table I). Mild to moderate phototoxicity occurred in 3 of 16 patients. None of the patients suffered from nausea after bathing in 8-MOP bath-water. No skin tumours were detected throughout the entire follow-up period.

Therapy cycles had a mean duration of 63.1 (±3.5) days. A mean of 29.4 (±1.4) irradiations with mean cumulative UVA doses of 33.3±3.3 J cm⁻² were administered per therapy cycle.

At the end of this study three patients were still in clinical remission 22, 58 and 74 weeks after one cycle of bath-water PUVA therapy. In 13 of 16 patients relapses occurred within the follow-up period. The mean

Table I. Patients' characteristics and results after one therapy cycle of bath-water PUVA with 8-methoxypsoralen (mean±SEM)

Variables	Outcome
Number of patients	16
Male	11
Female	5
Skin type	
II	6
III	10
Duration of MF (months)	2–156
Mean	40.6±12.3
Age range	21–73
Mean	53.2±3.9
Response rate	
Complete clinical response	16/16 (100%)
Duration of therapy (days)	63.1±3.5
Number of treatments	29.4±1.4
Patients	
With relapse	13 (81%)
In remission	3 (19%)
Time to relapse (weeks)	45.6±9.2
Cumulative UVA dose per therapy cycle (J/cm ²)	33.3±3.3
Phototoxic adverse events	3/16 (19%)

MF, mycosis fungoides.

disease-free interval after achieving complete clinical response was 45.6 weeks. In 5 of the 16 patients bath-water PUVA therapy was repeated after recurrence of the disease, in 4 patients after their first relapse, in 1 patient after a first and a second relapse of MF. Mean durations were 68.7 (±8.5) days, mean number of irradiations was 34.7 (±3.1) and mean cumulative UVA doses were 43.3 (±9.6) J cm⁻². Until the end of the follow-up period three of these five patients relapsed 26, 40 and 65 weeks (43.6±11.4) after the second bath-water PUVA therapy, two patients were still in remission 52 and 28 weeks after the second therapy. The patient who received a third therapy cycle was still in remission 18 weeks after the end of the last therapy cycle.

DISCUSSION

Oral PUVA has been shown to be effective in early MF in many studies and has thus become a standard regimen (5–10). More recently, bath-water PUVA emerged as a reasonable alternative to oral PUVA in both inflammatory and proliferative skin conditions. Lüftl et al. (27) observed complete clearance in 5 of 11 patients and marked clinical improvement in another 4 patients. Also Kerscher et al. (28) experienced a beneficial therapeutic effect of bath-water PUVA with 8-MOP in patients with MF. Although bath-water PUVA with 8-MOP has been included in guidelines for therapy of MF (29), a systematic investigation of this

treatment modality for this indication has not been performed yet.

In our study, this treatment regimen proved to be effective and resulted in complete clinical clearance in all patients. This high response rate is comparable to previous studies using oral 8-MOP PUVA treatment and bath-water PUVA with TMP. The initial report of Konrad et al. (4) demonstrated complete clearance in all of 15 patients with stage I or II MF with oral PUVA therapy using 8-MOP, while the cycle duration and the number of treatments were comparable to those of our study. Hönigsmann et al. (5) reported complete clinical remissions after 19 treatments and 50 days on average (maintenance therapy excluded) using a similar protocol with PUVA treatments four times weekly. Fischer & Skogh (23) reported on apparently normal or almost normal skin after 2–6 months of TMP bath-water PUVA in 14 of 15 patients with early MF.

Because of the high life expectancy of patients with early stage MF (26), survival is not an appropriate endpoint for the evaluation of early stage MF therapy. MF is a systemic disorder with relapses of the cutaneous patches months to years after clinical clearance. Thus, the disease-free time after therapy is a more appropriate outcome measure for early stage MF therapy.

At present, there is no uniformly accepted phototherapeutic modality for the treatment of early stage MF, and thus a great variety of therapeutic protocols is in use, which may explain variations in outcome reported from different centres. For example, for UVB phototherapy, disease-free intervals after complete clearing of MF vary between 6 and 51 months (30). Similarly, the results of oral PUVA with 8-MOP vary depending on treatment schedules and duration. Roenigk et al. (6) reported mean remission times of 13 months in stage IA and 11 months in stage IB following complete clearing (both including 18 weeks of maintenance therapy). In a follow-up study by Hönigsmann et al. (5), PUVA treatment four times weekly resulted in remission times between 8.5 and 21 months. In a study by Diederer et al. (30), PUVA treatment twice a week for mean time periods of 11 months resulted in mean disease-free periods of 22 months. In our bath-water PUVA study, those patients who relapsed displayed mean disease-free intervals of 45 weeks. The mean disease-free periods of five patients with early MF who had received oral 8-MOP at our unit during the time of this study, using exactly the same treatment schedule and the same PUVA cabinets, were somewhat shorter, i.e. 30 (± 3.5) weeks after complete clearance (mean duration of therapy: 64.5 days/25.8 treatments). With due respect to the inconsistencies of retrospective analyses and the discrepancies in the pertinent literature, our data suggest that remission times after bath-water PUVA in early MF are well in the range of those of oral PUVA, or possibly longer. Obviously, a prospective

comparative study with larger numbers of patients would be needed to clarify this point.

The exact mechanisms of PUVA therapy in MF are not known. PUVA treatment is believed to cause mitotic inhibition and/or induction of apoptosis in neoplastic T cells in the epidermis and superficial skin capillaries (30–32). It has also been shown that topical 8-MOP administration suppresses epidermal as well as superficial dermal lymphocyte function (33). We suggest that the cellular mechanism of action is the same or a similar one in systemic PUVA and topical PUVA therapy. However, doses of UVA and concentrations of 8-MOP in the epidermis and dermis are different in oral and bath-water PUVA therapy. This might explain the possibly different durations of mean relapse-free periods after these therapies.

Carcinogenicity is a major concern in both phototherapy and photochemotherapy. Lindelöf et al. (34) reported an increased risk for cutaneous squamous cell carcinoma (SCC) in men treated with oral 8-MOP PUVA. In that study, 4 of 18 SCCs induced by oral PUVA were located on the face. In bath-water PUVA therapy, the head and neck areas are not photosensitized and receive UVA only. While this may be a disadvantage for patients with head and/or neck involvement, it certainly contributes to a diminished carcinogenicity of bath-water PUVA.

Another large epidemiological study by Lindelöf et al. (35) raised the possibility that systemic PUVA may be associated with a higher risk for internal cancer (respiratory, pancreatic, colon and kidney). Also in this respect, bath-PUVA would obviously be safer than oral PUVA as 8-MOP serum levels are not detectable or extremely low in patients treated with bath-water PUVA (36).

In summary, our data suggest that bath-water PUVA with 8-MOP is a valuable alternative in photochemotherapy of MF, especially when systemic psoralen should be avoided. Clearance rates, duration of therapy and the number of irradiations required appear to be in the range of those in oral PUVA therapy. Major advantages are the absence of systemic photosensitization, shorter post-treatment photosensitivity and probably reduced photocarcinogenicity.

REFERENCES

1. Whittaker SJ, Marsden JR, Spittle M, Russell Jones R. Joint British Association of Dermatologists and U.K. Cutaneous Lymphoma Group guidelines for the management of primary cutaneous T-cell lymphomas. *Br J Dermatol* 2003; 149: 1095–1107.
2. Dummer R, Kempf W, Hess Schmid M, Häffner A, Burg G. Therapy of cutaneous lymphoma – current practice and future developments. *Onkologie* 2003; 26: 366–372.
3. Gilchrist BA, Parrish JA, Tanenbaum L. Oral methoxypsoralen photochemotherapy of mycosis fungoides. *Cancer* 1976; 38: 683–689.

4. Konrad K, Gschnait F, Hönigsmann H, Fritsch P, Wolff K. Photochemotherapy in mycosis fungoides. *Hautarzt* 1978; 29: 191–197.
5. Hönigsmann H, Brenner W, Rauschmeier W, Konrad K, Wolff K. Photochemotherapy for cutaneous T-cell lymphoma. *J Am Acad Dermatol* 1984; 10: 238–245.
6. Roenigk H, Kuzel T, Skoutelis A, Springer E, Yu G, Caro W, et al. Photochemotherapy alone or combined with interferon alpha-2a in the treatment of cutaneous T-cell lymphoma. *J Invest Dermatol* 1990; 95: 198S–205S.
7. Holloway KB, Flowers FP, Ramos-Caro FA. Therapeutic alternatives in cutaneous T-cell lymphoma. *J Am Acad Dermatol* 1992; 27: 367–378.
8. Herrmann JJ, Roenigk HH Jr, Hurria A, Kuzel TM, Samuelson E, Rademaker AW, et al. Treatment of mycosis fungoides with photochemotherapy (PUVA): long-term follow-up. *J Am Acad Dermatol* 1995; 33: 234–242.
9. Roupe G, Sandström MH, Kjellström C. PUVA in early mycosis fungoides may give long-term remission and delay extracutaneous spread. *Acta Derm Venereol* 1996; 76: 475–478.
10. Watson A. Photochemotherapy for mycosis fungoides: current status. *Australas J Dermatol* 1997; 38: 9–11.
11. Fischer T, Alsins J. Treatment of psoriasis with trioxsalen baths and dysprosium lamps. *Acta Derm Venereol* 1976; 56: 383–390.
12. Lowe NJ, Weingarten D, Bourget T, Moy LS. PUVA treatment for psoriasis: comparison of oral and bath-water delivery of 8-methoxypsoralen. *J Am Acad Dermatol* 1986; 14: 754–760.
13. Salomon N, Walchner M, Messer G, Plewig G, Röcken M. Bath-PUVA therapy of granuloma annulare. *Hautarzt* 1999; 50: 275–279.
14. Der-Petrossian M, Seeber A, Honigsmann H, Tanew A. Half-side comparison study on the efficacy of 8-methoxypsoralen bath-PUVA versus narrow-band ultraviolet B phototherapy in patients with severe chronic atopic dermatitis. *Br J Dermatol* 2000; 142: 39–43.
15. von Kobyletzki G, Gruss C, Altmeyer P, Kerscher M. Balneophotochemotherapy of lichen ruber. Personal results and comparison with photochemotherapy modalities employed up to now. *Hautarzt* 1997; 48: 323–327.
16. von Kobyletzki G, Freitag M, Hoffmann K, Altmeyer P, Kerscher M. Balneophotochemotherapy with 8-methoxypsoralen in lichen sclerosus et atrophicus. *Hautarzt* 1997; 48: 488–491.
17. Kerscher M, Volkenandt M, Meurer M, Lehmann P, Plewig G, Röcken M. Treatment of localised scleroderma with PUVA bath photochemotherapy. *Lancet* 1994; 343: 1233.
18. Schempp CM, Müller H, Czech W, Schopf E, Simon JC. Treatment of chronic palmoplantar eczema with local bath-PUVA therapy. *J Am Acad Dermatol* 1997; 36: 733–737.
19. Behrens S, von Kobyletzki G, Gruss C, Reuther T, Altmeyer P, Kerscher M. PUVA-bath photochemotherapy (PUVA-soak therapy) of recalcitrant dermatoses of the palms and soles. *Photodermatol Photoimmunol Photomed* 1999; 15: 47–51.
20. Kowalczick L, Ott A, Waldmann T, Suckow M, Pönnighaus JM. Therapy of lymphomatoid papulosis with balneo-PUVA-photochemotherapy. *Hautarzt* 2000; 51: 778–780.
21. Collins P, Rogers S. Bath-water compared with oral delivery of 8-methoxypsoralen PUVA therapy for chronic plaque psoriasis. *Br J Dermatol* 1992; 127: 392–395.
22. Cooper EJ, Herd RM, Priestly GC, Hunter JA. A comparison of bathwater and oral delivery of 8-methoxypsoralen in PUVA therapy for plaque psoriasis. *Clin Exp Dermatol* 2000; 25: 111–114.
23. Fischer T, Skogh M. Treatment of parapsoriasis en plaques, mycosis fungoides, and Sezary's syndrome with trioxsalen baths followed by ultraviolet light. *Acta Derm Venereol* 1979; 59: 171–173.
24. Fitzpatrick TB. The validity and practicality of sun-reactive skin types I through IV. *Arch Dermatol* 1988; 124: 869–871.
25. Bunn PJ, Lamberg S. Report of the committee on staging and classification of cutaneous T-cell lymphomas. *Cancer Treat Rep* 1979; 63: 725–728.
26. Kim YH, Jensen RA, Watanabe GL, Varghese A, Hoppe RT. Clinical stage IA (Limited patch and plaque) mycosis fungoides. *Arch Dermatol* 1996; 132: 1309–1313.
27. Lüftl M, Degitz K, Plewig G, Röcken M. Psoralen bath plus UVA-therapy. *Arch Dermatol* 1997; 133: 1597–1603.
28. Kerscher M, Lehmann P, Plewig G. PUVA-Bad-Therapie. *Hautarzt* 1994; 45: 526–528.
29. Röcken M, Plewig G. Bad-PUVA-Photochemotherapie. In: Krutmann J, Hönigsmann H, editors. *Handbuch der dermatologischen Phototherapie und Photodiagnostik*. Berlin: Springer, 1997: 259–279.
30. Diederer P, van Welden H, Sanders C, Toonstra J, van Vloten WA. Narrowband UVB and psoralen-UVA in the treatment of early-stage mycosis fungoides: a retrospective study. *J Am Acad Dermatol* 2003; 48: 215–219.
31. Gilchrist BA. Methoxsalen photochemotherapy for mycosis fungoides. *Cancer Treat Rep* 1979; 63: 663–667.
32. Yoo EK, Rook AH, Elenitsas R, Gasparro FP, Vowels BR. Apoptosis induction by ultraviolet light A and photochemotherapy in cutaneous T-cell lymphoma: relevance to mechanism of therapeutic action. *J Invest Dermatol* 1996; 107: 235–242.
33. Vallat V, Gilleaudeau P, Battat L, Wolfé J, Nabeya R, Heftler N, et al. PUVA-bath therapy strongly suppresses immunological and epidermal activation in psoriasis: a possible cellular basis for remittive therapy. *J Exp Med* 1994; 180: 283–296.
34. Lindelöf B, Sigurgeirsson B, Tegner E, Larkö O, Berne B. Comparison of the carcinogenic potential of trioxsalen bath PUVA and oral methoxsalen PUVA. *Arch Dermatol* 1992; 128: 1341–1344.
35. Lindelöf B, Sigurgeirsson B, Tegner E, Larkö O, Johannesson A, Berne B, et al. PUVA and cancer: a large scale epidemiologic study. *Lancet* 1991; 338: 91–93.
36. David M, Lowe N, Halder R, Borok M. Serum 8-methoxypsoralen (8-MOP) concentrations after bath-water delivery of 8-MOP plus UVA. *J Am Acad Dermatol* 1990; 23: 931–932.