Long-term Follow-up of Photodynamic Therapy for Mycosis Fungoides

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Sir,

Mycosis fungoides (MF) is a primary, cutaneous, T-cell lymphoma characterized by slow progress over years or decades, developing from patches to more infiltrated plaques and sometimes to tumours (1). The incidence per general population of cutaneous lymphomas is estimated as 0.4–1 in 100,000 per year (2, 3).

Patients with patch/plaque-stage MF and less than 10% of the skin involved have survival rates similar to that of an age-, sex-, and race-matched population (4). Survival rates decrease with the area of skin involvement and with more infiltrated lesions such as tumour-stage MF (4, 5).

There is no curative treatment for MF. Topical therapy, such as corticosteroids, nitrogen mustard or carmustine, photochomotherapy (psoralen+ultraviolet A; PUVA), radiotherapy, immunotherapy, chemotherapy, monoclonal antibody therapy and novel retinoids, can be used (3). Photodynamic therapy (PDT) has been used in several cases, but without long-term follow-up (6–15; Table I).

We performed a long-term (6–9 years) follow-up of 10 patients with plaque-stage MF treated with PDT.

MATERIALS AND METHODS

Ten patients with MF (6 men and 4 women, mean age 67 years, age range 58–81 years) participated in the study and received PDT treatment during 1995 to 1999. In 2 patients, 2 lesions were treated. Ten lesions were at the plaque stage of MF and 2 were tumour stage MF. The diagnosis was confirmed with routine histopathology and immunophenotyping. Only one patient (no. 3; Table II) had enlarged lymph nodes on the neck (tumour, node, metastasis (TNM) classification T1, N1, M0). The other patients had no signs of internal involvement. More patient characteristics are shown in Table II and further information is given in the previous publication (13).

Twenty percent 5-aminolevulinic acid (ALA) (Phorpyrin Products, Utah, USA), dissolved in an oil-water emulsion, was applied topically to the lesion and to adjacent skin under an occluding and light-shielding dressing for 5–6 h. The red fluorescence of porphyrins was visualized with Wood's light before treatment. The ALA-treated areas were then exposed to incoherent light using a Waldmann PDT 1200 (Waldmann Medical Division, Villingen-Schwenningen, Germany) and emitting light at a wavelength of 600–730 nm with a maximum around 630 nm. The patients were treated with intervals of 1–2 weeks, 2–11 times (median 2.5 times) (Table II). The first follow-up, at 4–21 months after the last PDT, showed clinically complete clearance in 7 of 9 plaque lesions (13). Biopsies were taken after treatment in 9 patients. Histological evaluation and CD3 staining confirmed a significant regression of the infiltrate in all cases studied. In clinically responding lesions, the biopsies showed no remaining atypical infiltrates (13). The 2 tumour-stage MFs did not respond to treatment.

The follow-up reported in this study was performed during 2004 to 2005. Patients were examined on the area previously treated with PDT and a 4-mm punch biopsy was taken. The biopsy was formalin-fixed and embedded in paraffin. For histological evaluation, routine haematoxylin-eosin-stained sections were used.

The study was approved by the local ethics committee.

RESULTS

This second follow-up was performed between 5 years and 11 months and 8 years and 10 months after the last PDT, with a median interval of 7.25 years.

Three of the 7 patients with plaque MF who showed clinical and histological clearance in the first follow-up had died before the second follow-up. All 3 patients had developed tumour-stage MF with metastasis, but not in the areas previously treated with PDT, according to clinical information collected from the hospital records (Table II).

The other 4 patients (no. 1, 5, 7 and 9) had no relapse of MF in the area treated with PDT. Three of the healed patients had received no further treatment for MF (no. 5, 7 and 9). The fourth patient had been treated with methotrexate, retinoids, interferon, PUVA, UVA1 (long-

Table I. *Summary of published studies using photodynamic therapy (PDT) for mycosis fungoides*

Reference	No. of lesions	Stage	No. of PDT	Lesions in remission (%)	Clinical follow-up	Histological follow-up
Svanberg et al. (6)	4	Not reported	1–2	2 (50)	6–14 months	Not reported
Wolf et al. (7)	3	Plaque	4–5	3 (100)	3–6 months	6 weeks
Ammann (8)	1	Plaque	1	None (0)	24 days	24 days
Eich et al. (9)	2	Tumour	12	2 (100)	24 months	2 weeks
Orenstein et al. (10)	1	Patch	1	1 (100)	27 months	3 months
	5	Tumour	1	5 (100)	24 months	3 months
Markham (11)	1	Tumour	5	1 (100)	12 months	Was done
Leman et al. (12)	2	Plaque	4	2 (100)	12 months	6 weeks
Coors et al. (14)	1	Plaque	2	1 (100)	18 months	Not done
	3	Plaque	6–7	3 (100)	14 months	
Zane et al. (15)	5	Patch	1–9	4 (80)	12–34 months	End of treatment

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Table II. *Characteristics of patients, mycosis fungoides (MF) lesions, photodynamic therapy (PDT) and clinical results*

Patient number/ gender	Previous treatment	MF lesion	Location of lesion	Fluence (J/cm^2)	No. of PDTs	First follow-up	After first follow-up	Second follow-up
1/M	PUVA	Plaque	Thigh	90	2	Healed	PUVA, UVA1,	Healed
	PUVA	Plaque	Hip	50+30	2	Regression	Radiotherapy, methotrexate Interferon	
2/M	Local steroids	Plaque	Hip	180	2	Healed	Developed tumour MF in the face	Died 2003
3/M	PUVA	Tumour	Trunk	180	3	No response	Developed tumour MF on the leg	Died 1998
	PUVA	Plaque	Back	180	3	Healed		
4/F	PUVA	Plaque	Thigh	90	2	Healed	Developed tumour MF on lower leg and in face	Died 2001
5/M	None	Plaque	Gluteal	50+60	2	Healed	No treatment	Healed
6/M	None	Plaque	Gluteal	90	8	No response		
7/M	Radiotherapy PUVA	Plaque	Arm	90	11	Healed	No treatment	Healed
8/F	PUVA	Tumour	Abdomen	100	3	No response		
9/F	PUVA	Plaque	Trunk	90	3	Healed	No treatment	Healed
10/F	PUVA	Plaque	Thigh	90+50	2	Regression		

PUVA: psoralen plus ultraviolet A.

wave-ultraviolet-A radiation) and local radiotherapy to the face, buttock, thigh and neck.

All 4 patients fulfilled the criteria for cutaneous lymphoma of MF type in routine histological examination prior to PDT. The biopsies taken at the second follow-up showed loss of lymphocytic infiltrate in all 4 patients.

DISCUSSION

Svanberg et al. (6) showed already in 1994 a clinically complete response in 2 of 4 lesions of T-cell lymphomas treated once or twice with PDT (see Table I).

Eich et al. (9) treated a patient with tumour-cutaneous T-cell lymphoma with 8 sessions of PDT. Biopsy showed remission at 1.5 mm depth, but an infiltrate of lymphocytes remained deeper in the skin. The second patient with a tumour MF was treated with 12 PDT sessions. Biopsy taken 2 weeks after completed PDT showed no infiltrate of lymphocytes. The patient was followed up at 24 months with no clinical relapse, but was also treated with PUVA and interferon during that time.

Our experience is that PDT is not efficient on tumour MF. This might be due to lack of penetration of the ALA and/or the light. Zane et al. (15) used methylaminolevulinate (MAL) for treating patch stage MF. MAL has a higher penetration because of its increased lipophilic properties.

Our study started in 1995 when little was known about the optimal fluence. Initially, a fluence of 180 J/cm^2 was given, but this had to be halved because of troublesome pain. However, even patients treated with lower fluences healed, suggesting that higher fluence should be avoided because of more pain.

We noticed that the treatment of larger plaque lesions with a diameter of 7.5 cm or more was less successful (see Table II). One large lesion healed, but had to be treated 11 times (no. 7). Two patients with larger MF plaques lesions (nos. 1 and 10) showed a regression, but did not heal completely. Patient no. 10 discontinued PDT because of pain. That treatment of larger skin tumours results in more pain is an old observation (16). This might be an effect of more malignant cells accumulating photosensitizing protoporphyrin in the target cells.

Prior to this study, the longest clinical follow-up (1–3 years) is reported by Zane et al. (15), but they had no histological follow-up. We had 4 patients with clinical and histological MF in remission at the area treated with PDT. Three of these had not received any other treatment. The fourth patient had had several other treatments and is therefore difficult to evaluate, but no new lesions developed in the area treated with PDT. Three patients who were healed at the PDT location died 2–7 years later. It is interesting to note that none of these developed a tumour MF in the region of PDT.

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