Bath-PUVA Therapy Decreases Infiltrating CCR4-Expressing Tumor Cells and Regulatory T Cells in Patients With Mycosis Fungoides

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Abstract

In this study, we analyzed the mechanism that bath-PUVA therapy to CCR4-expressing tumor cells and regulatory T cells (Treg) in patients with mycosis fungoides(MF). The CCR4 positive cell and Treg in patient blood and the skin were analyzed. Both type of cells decreased after bath-PUVA in the skin lesion, in contrast, bath-PUVA did not significantly change the percent circulating Treg. It suggested that bath-PUVA eliminated both pathogenetically relevant cells and Treg and systemic immunosuppression was not induced.

Background: Mycosis fungoides (MF) is a malignant lymphoma characterized by expansion of $CD4^+$ memory T-cell clones. Infiltrating cells express CCR4, which is attracted to CC chemokine ligands 17 and 22 (thymus and activation-regulated chemokine [TARC]/CCL17 and TARC/CCL22). Bath–psoralen plus ultraviolet A (PUVA) is effective against MF. In patients with psoriasis, bath-PUVA induces circulating regulatory T cells (Tregs), which suppress effector T cells. To understand the mechanisms in MF, we analyzed lesion-infiltrating cells before and after bath-PUVA therapy. **Patients and Methods:** Thirteen patients with MF (12 stage IB, 1 stage III; mean age 69.2 years, range 35-87 years; 6 men, 7 women) were recruited. **Results:** Immunohistochemical analysis revealed that lesion CCR4-positive ($CCR4^+$) cells and Tregs significantly decreased from 105.1 ± 164.8 cells/10^{-2} mm^2 to 31.4 ± 39.0 cells/10^{-2} mm^2 and from 78.1 ± 67.8 cells/10^{-2} mm^2 to 24.7 ± 25.0 cells/10^{-2} mm^2, respectively. Serum TARC levels significantly correlated with infiltrating $CD3^+$ ($r = 0.997$), $CCR4^+$ ($r = 0.991$), and forkhead box P3–positive ($Foxp3^{+}$) cells ($r = 0.843$). Circulating Tregs before bath-PUVA therapy were not significantly different from those in healthy volunteers. Bath-PUVA did not significantly change the percentage of circulating Tregs. **Conclusions:** Bath-PUVA decreased $CCR4^+$ cells and Tregs in MF lesions but did not induce circulating Tregs, which might suppress effector T cells. Direct effects through skin lesions might eliminate both pathogenetically relevant cells and Tregs. Systemic immunosuppression was not induced.

Clinical Lymphoma, Myeloma & Leukemia, Vol. 13, No. 3, 273-80
Keywords: Bath-PUVA therapy, CCR4, Mycosis fungoides, Regulatory T cell, Thymus and activation-regulated chemokine (TARC)

Introduction

Mycosis fungoides (MF) is a malignant cutaneous lymphoma with a chronic disease progression.[1] Because erythema and red plaques appear on the patient's whole body at an early stage, it is important to distinguish MF from other skin diseases. Various symptoms are associated with MF, including lymph node enlargement, skin tumors, and ulcer formation in the tumor stage. Symptom onset usually occurs in those older than 60 years of age, but the actual disease onset is earlier.[2] The histologic findings depend on the stage. In the erythema stage (stage I), the characteristic features include epidermal hyperplasia, lymphoid exocytosis, and band-like lymphoid infiltration in the

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Submitted: Aug 21, 2012; Revised: Nov 29, 2012; Accepted: Dec 8, 2012; Epub: Jan 16, 2013

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2152-2650/$ - see frontmatter
http://dx.doi.org/10.1016/j.clml.2012.12.002

Table 1 Patient Characteristics

Patient	Age	Sex	Disease Stage	Irradiation Frequency	Cumulative UV Doses (J/cm^2)
1	82	F	IB	46	170.4
2	68	F	III	42	146.4
3	35	F	IB	43	53.7
4	71	M	IB	20	45.0
5	87	M	IB	33	120.0
6	82	M	IB	5	8.0
7	77	M	IB	29	106.0
8	70	F	IB	37	138.0
9	83	M	IB	38	138.0
10	62	F	IB	14	29.5
11	56	M	IB	30	106.0
12	64	F	IB	42	150.0
13	62	F	IB	25	34.5
Mean ± SD	69.2 ± 14.1			31.1 ± 12.3	95.8 ± 54.5

Abbreviations: SD = standard deviation; UV = ultraviolet.

Figure 1 Immunohistochemical Analysis for Before Bath–Psoralen Plus Ultraviolet A (PUVA) Therapy. Hematoxylin and Eosin Stain (A), Anti-CD3 (B), Anti-CCR4 (C), Anti-Foxp3 (D). A Pautrier Microabscess was Observed in the Epidermis. Many CCR4$^+$ Lymphocytes Were Observed. In Contrast, There Were a Few Foxp3$^+$ Cells. Yellow Triangles Were Some of Positive Cells