Effect of Narrowband Ultraviolet B with Methotrexate on T Cell Receptor Gamma Gene Rearrangement in the Skin and Blood of Mycosis Fungoides Patients

Thesis

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Abstract

Mycosis fungoides (MF) is the most common subtype of cutaneous T cell lymphomas (CTCLs). T cell receptor (TCR) γ gene rearrangement, demonstrated by polymerase chain reaction (PCR), is the most effective method to evaluate clonality in T cell malignant neoplasms. The aim of this study was to determine whether the presence of a dominant T cell clone in the blood of stage IA and IB MF patients is associated with more severe clinical picture and/or resistance to therapy, which was previously investigated but on all stages of MF including Sézary syndrome (SS) "collectively", and to investigate the PCR outcome in the skin and blood after treatment with narrowband ultraviolet B (NB-UVB) combined with methotrexate. Thirty participants with stage I MF were included in this study. They received 36 NB-UVB sessions (3 sessions/week) in combination with methotrexate tablets 0.3 mg/kg/week for 3 months. Participants were evaluated before and after treatment regarding clinical picture, epidermotropism, density of dermal infiltrate, skin and blood examination for TCR γ gene rearrangement by PCR. A dominant T cell clone was detected in the skin of 21/28 (75%) of participants and disappeared from 9/21 (42.8%) after treatment. Regarding the blood, a dominant T cell clone was detected in 14/28 (50%) of participants and disappeared from 6/14 (42.8%) after treatment. Participants were divided into 2 groups according to pre-treatment blood PCR: group I (negative) and group II (positive). Our results demonstrated that collectively, both negative post-treatment skin PCR and negative post-treatment blood PCR were significantly associated with better clinical outcome and less dense post-treatment dermal infiltrate. However, they could not show the prognostic value of pre-treatment skin or blood PCR in the prediction of post-treatment clinical and histopathological outcome.

Key words: Mycosis fungoides-TCR γ gene rearrangement-clonality-prognosis

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List of Abbreviations

BB	broadband
C	constant
CBC	complete blood count
CCL	chemokine ligands
CCR	chemokine receptor
cDNA	complementary deoxyribonucleic acid
CDR	complementarity determining region
CLA	cutaneous lymphocyte antigen
CMV	cytomegalovirus
CT	computed tomography
CTCL	cutaneous T cell lymphoma
D	diversity
DNA	deoxyribonucleic acid
EBV	Epstein-Barr virus
ECP	extracorporeal photopheresis
EORTC	European organization for research and treatment of cancer
FDA	Food and Drug Administration
FST	Fitzpatrick skin type
HIV	human immunodeficiency virus
HTLV	human T-cell lymphotropic virus
IL	interleukin
ISCL	international society for cutaneous lymphoma
J	joining
LN	lymph node
MED	Minimal erythema dose
MF	Mycosis fungoides
MHC	major histocompatibility complex
NB	Narrowband

NCI	National Cancer Institute
NSAIDs	non-steroidal anti-inflammatory drugs
PCR	polymerase chain reaction
PUVA	psoralen plus ultraviolet A
RAG	Recombinase activating gene
SB	Southern blotting
SS	Sézary syndrome
TBI	tumor burden index
TCR	T-cell receptor
TdT	terminal deoxyribonucleotidyl transferase
TGF	transforming growth factor
Th2	T-helper 2
TNF	tumor necrosis factor
TNM	tumor-node- metastasis
TNMB	tumor-node- metastasis-blood
TSEBT	total skin electron beam therapy
UV	ultraviolet
V	variable
WBC	white blood cell

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INTRODUCTION

Cutaneous T cell lymphomas (CTCLs) are a group of diseases characterized by several features, including the proliferation of skin homing T-cells, the monoclonal nature of these T-cells and the potential of almost all forms to transform into high grade T-cell lymphoma ***(Girardi et al., 2004)***. Mycosis fungoides (MF) is the most common variant of primary CTCL, generally associated with an indolent clinical course and characterized by well-defined clinicopathological features ***(Whittaker and Mackie, 2004).***

Although the disease is limited to the skin in its early manifestations, it was reported that 50% of patients with early disease have clones of T cells in their blood ***(Hwong et al., 2001)***.

All the tumor cells carry an identical T-cell receptor (TCR), a marker that can be used for diagnostic and prognostic monitoring ***(Berger et al., 1998).***

The TCR is the antigen-specific receptor for T cells. During differentiation, each T cell undergoes rearrangement of its TCR genes. This results in novel nucleotide sequences that constitute a unique signature or fingerprint for each T cell and all its clonal progeny ***(Wood, 2001a).***

Several studies reported that patients with dominant T cell clones detected by polymerase chain reaction (PCR) in the skin and/or blood have a worse prognosis ***(Delfau-Larue et al., 1998a & Fraser-Andrews et al., 2000 & Beylot-Barry et al., 2001 & Vega et al., 2002).***

The choice of initial treatment for the MF patient depends on the stage of the disease as well as the general condition and age of the patient. There are very few published studies that could form the basis for evidence-based therapy, mainly because of the variation between individual patients in disease pattern and progress ***(Whittaker and MacKie, 2004).***

Narrowband ultraviolet B (NB-UVB) therapy is an effective modality for patients with early-stage MF ***(Diederen et al., 2003).***

Low-dose methotrexate has been shown to be particularly effective in patients with erythrodermic MF ***(Zackheim et al., 1996),*** in addition, its use has been suggested for refractory early-stage ***(Zackheim et al., 2003)*** as well as in stage IB MF ***(McFarlane et al., 2005).***

Aim of work:

The aim of this study was to determine whether the presence of a dominant T cell clone in the blood of stage IA and IB MF patients is associated with more severe clinical picture and/or resistance to therapy, which was previously investigated but on all stages of MF including SS "collectively", and to investigate the PCR outcome in the skin and blood after treatment with NB-UVB combined with methotrexate.