Vorinostat in Combination Therapy of Sézary Syndrome with Extracorporeal Photopheresis

O Akilov, L Geskin

Citation

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Abstract

Vorinostat, the first in its class of orally administered histone deacetylase inhibitors, was recently FDA-approved for therapy of skin manifestations of cutaneous T cell lymphoma. Vorinostat monotherapy demonstrated activity in patients with CTCL in clinical trials with an overall response rate of 30%. The combination of vorinostat with other agents or treatment modalities has not been formally evaluated. We hypothesized that the use of vorinostat in combination with extracorporeal photopheresis might be of benefit, theoretically through further induction of cell cycle arrest and apoptosis of malignant T lymphocytes. We present a case report of a patient with refractory Sézary syndrome who responded well to this combination without significant or unexpected side effects.

Dr. Larisa Geskin, MD, FAAD is an Assistant Professor of Dermatology at the Department of Dermatology, University of Pittsburgh School of Medicine. Dr. Geskin serves as the Director of the Dermatological Branch of University of Pittsburgh Cancer Institute Multidisciplinary Melanoma Center, the Cutaneous Oncology and Photopheresis Center at the University of Pittsburgh Medical Center. She also is Director of the Dermatology Residency Program at the University of Pittsburgh Medical School.

Dr. Larisa Geskin's broad research interests include exploring etiology of CTCL and abnormalities found in malignant cells of patients with CTCL. Her main focus is to investigate and define immunologic abnormalities found in patients with CTCL and to develop novel immunologic therapies for CTCL. She conducts numerous clinical trials investigating new treatments for CTCL, including a dendritic cell vaccine trial for patients with Sezary syndrome.

INTRODUCTION

Sézary syndrome (SS) is an erythrodermic and leukemic variant of cutaneous T-cell lymphoma. The disease may have an aggressive character and poor outcome (the 5-year overall survival historically was between 10-20%) [1]. Timely and effective palliative therapy remains a cornerstone in the management of these patients.

Vorinostat, a novel histone deacetylase inhibitor (HDACi), has been shown to have up to a 30% response rate in heavily pretreated and recalcitrant patients with CTCL; it has an acceptable side effect profile and was not associated with opportunistic infections in clinical trials, thus making it a good candidate for long-term therapy for patients with impaired immunity. The mechanism of action of HDACi is broad, including the increased acetylation of lysine residues that form the octomeric histone core of chromatin decreasing the ability of the histones to bind to DNA. This decreased binding allows chromatin expansion, permitting transcription, which regulates cell proliferation and cell death. Other potential targets, which may be important in induction of clinical responses in patients, are acetylation of non-histone proteins affecting other intracellular processes including chaperone-mediated protein transport, mitosis, oncogene and tumor suppressor gene expression, thus regulating cell proliferation and cell death [2, 3]. CTCL has been shown to be the neoplasm most responsive to HDACi to date [4].

Extracorporeal photopheresis (ECP) is one of the first line therapies for SS [5]. An intercalation of 8-methoxypsoralen into the DNA upon exposure to UVA light during ECP creates a pro-apoptotic environment modifying immune responses [6]. We hypothesized that a combination of ECP and HDACi may improve clinical outcome, theoretically through increasing the level of apoptosis of atypical T lymphocytes. We present a case report of use of vorinostat in combination with ECP resulting in improved clinical

outcome. Modest response rate of vorinostat as a monotherapy and its potential for synergy with other agents warrants further investigation.

CASE REPORT

A 38-year-old white female with a 3-year history of lymphadenopathy, rash, and markedly atypical lymphocytosis in peripheral blood was diagnosed with SS, stage IVA (T4N1B2M0) in 2000. Flow cytometry demonstrated that the lymphocytes were almost exclusively memory type CD4+CD45RO+ □□ T-cells, with weak CD25+ expression. There were virtually no B-cells present. Biopsy of an inguinal lymph node revealed very prominent diffuse interfollicular expansion by a proliferation of small to intermediate size lymphoid cells with very irregular nuclear contours and occasional nucleoli. PCR analysis demonstrated a T-cell receptor □-chain gene rearrangement (amplified with V9 region primers).

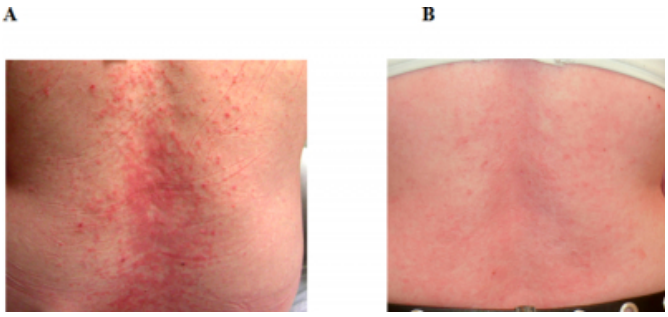
The patient had numerous therapies over the past several years, including ECP and interferon-□2a combination, denileukin diftitox, and gemcitabine without significant improvement. In 2003, she was treated with ECP and bexarotene with resolution of erythroderma and pruritus, but relapsed in 2005 with worsening of the generalized erythroderma, erythematous papules on her face, anterior and posterior neck, occipital scalp, upper chest, anterior shoulders, and mid-upper back (Fig. 1A).

Physical examination also revealed fissures of the palms and soles, generalized non-tender lymphadenopathy and multiple excoriations with impetiginization. Repeated peripheral blood smear revealed less than 5% lymphoid cells with irregular nuclear contours. Bexarotene was discontinued and vorinostat (400 mg) was initiated in addition to monthly ECP treatments. Within 2 weeks the patient noticed resolution of pruritus. Six weeks after beginning of treatment she developed a transient pruritic erythematous maculopapular follicular rash on her face, neck, and upper torso. Histological examination revealed follicular mucinosis, which resolved within 6 months of therapy. Significant clinical response was noticed within 3 months with nearly complete resolution of erythroderma and lymphadenopathy (Fig. 1B). The patient sustained clinical response for 6 months at which point the dose had to be modified due to gastrointestinal side effects, and she experienced a relapse of her disease.

Overall, this combination of vorinostat and ECP was well tolerated. The adverse events included mild taste changes, occasional fatigue, episodes of nausea, and overall 6-pound weight loss over the 4-month period. There were no unexpected or serious adverse events.

Figure 1

Figure 1. Visible improvement in cutaneous manifestations of the patient with refractory Sezary syndrome receiving combination of ECP and vorinostat; A) Before the combination therapy; B) Four months after initiation of vorinostat-ECP combination.



DISCUSSION

HDACi have been shown to have activity in patients with CTCL. The mechanism of action of HDACi may be broad, affecting various intracellular processes. HDACi showed synergistic activity with number of agents in preclinical studies. Combination of HDACi with other pro-apoptotic agents may result in superior anti-tumor activities compared to those observed using single agent [7]. We presented a case report which suggests that combinational therapy of ECP with vorinostat may provide such benefit and synergy clinically, which in our patient resulted in resolution of CTCL lesions.

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Author Information

Oleg E. Akilov, MD, PhD
Instructor, University of Pittsburgh School of Medicine, Department of Dermatology

Larisa Geskin, MD, FAAD
Assistant Professor of Dermatology, University of Pittsburgh School of Medicine, Department of Dermatology Director, Cutaneous Oncology and Photopheresis Unit Dermatology Residency Program Director