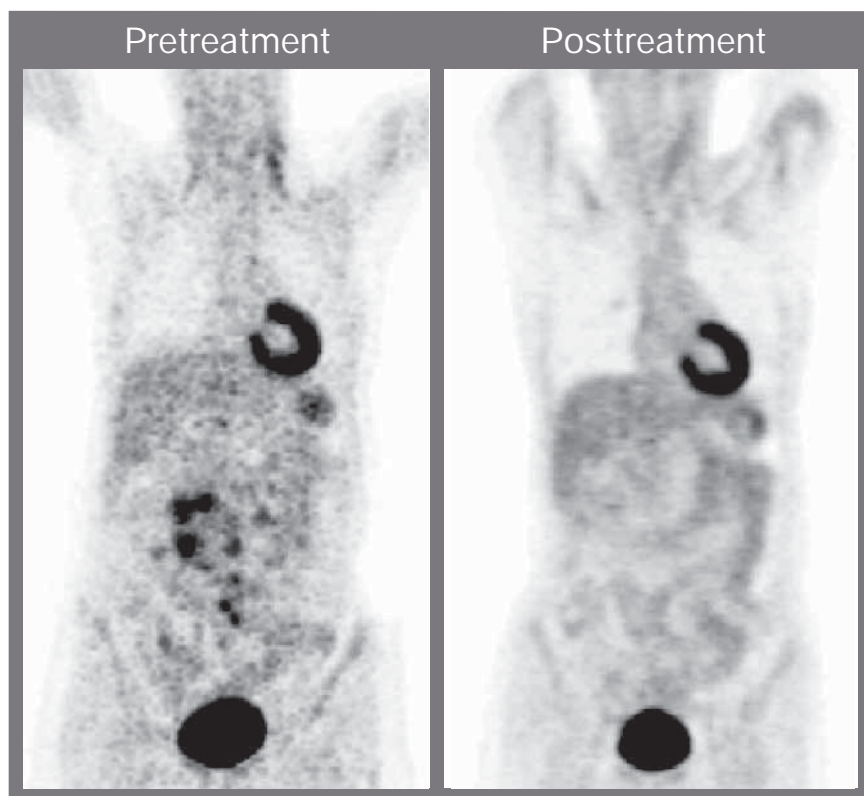


Case Studies in Lymphoma

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A Patient With Peripheral T-Cell Lymphoma Treated With a Histone Deacetylase Inhibitor

Richard L. Piekarz, MD, PhD

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Cover Illustration: Positron emission tomography scans of a patient with peripheral T-cell lymphoma revealing lymphadenopathy prior to romidepsin therapy (left panel) and reduction in lymphadenopathy after 8 months of romidepsin therapy (right panel)

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Overview and Purpose

T-cell lymphomas (TCLs), which include cutaneous TCL and peripheral TCL (PTCL), account for 10% of all non-Hodgkin lymphomas and are challenging malignancies to treat due to disease heterogeneity, chemotherapy resistance, and lack of available targeted therapies. While standard first-line therapy for PTCL is similar to that used to treat B-cell lymphomas, no standard second-line therapy exists for PTCL. However, second-line therapeutic options have been developed and are under investigation in that disease, including anti-CD52 antibodies, proteasome inhibitors, chemotherapeutic agents, and immunotoxins. Histone deacetylase inhibitors (HDACIs) also represent a new class of agents that have demonstrated clinical efficacy and a manageable toxicity profile in patients with PTCL.

The purpose of this activity is to update physicians on the use of HDACIs in the treatment of patients with PTCL.

Learning Objectives

Upon completion of this educational activity, you should be able to:

- Outline the safety of HDACIs in PTCL
- Summarize the recommended treatment options for patients with relapsed/refractory PTCL
- Evaluate the efficacy of HDACIs in PTCL

Target Audience

This publication is intended for medical oncologists and hematologists involved in the care of patients with peripheral T-cell lymphoma. No specific skills or knowledge other than a basic training in oncology is required for successful participation in this activity.

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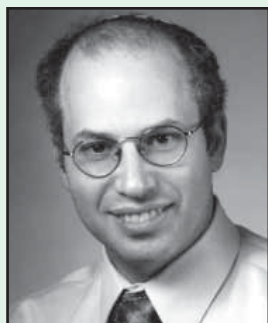
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A Patient With Peripheral T-Cell Lymphoma Treated With a Histone Deacetylase Inhibitor

Introduction

T-cell lymphomas (TCLs) comprise approximately 10% of all cases of non-Hodgkin lymphoma (NHL).^{1,2} T-cell NHL has been categorized separately from B-cell NHL, the more common form of NHL. In general, TCL is associated with a poorer prognosis. Although effective second-line therapy exists for B-cell lymphoma, there is no standard second-line therapy for peripheral TCL (PTCL).

Case Report

A 55-year-old woman with PTCL that recurred after standard CHOP (cyclophosphamide/doxorubicin/vincristine/prednisone) chemotherapy presented to the National Cancer Institute (NCI) for evaluation for protocol therapy. Her family history included multiple myeloma leading to death in her mother and colon and prostate cancer in her father. Personal medical history revealed nothing notable. The patient initially presented in 2001 to her home physician with limited-stage PTCL found in a cervical neck lymph node. She received CHOP and involved-field radiation therapy. After approximately 18 months, she returned with disease recurrence and enrolled in a phase II trial of romidepsin for patients with TCL.¹

Preprotocol computed tomography (CT) scan revealed cervical, mesenteric, and retroperitoneal lymphadenopathy. Positron emission tomography (PET) scan revealed uptake in the neck and multiple foci throughout the abdomen, consistent with the findings of the CT scan. Flow cytometry analysis performed on peripheral blood identified a population of cells that stained positive for CD4, CD5, and CD52 but negative for CD7, CD8, and CD25. This population represented < 0.6% of the white blood cells or an estimated 40 cells/ μ L. While this was interpreted as being involved with the patient's lymphoma, molecular analysis revealed 3 faint bands, none similar to the one detected in the patient's lymph node, which was considered to be a clonally restricted pattern. The identification of an aberrant T-cell population that is clonally restricted and distinct from the clone found in the lymphoma has been noted in a variety of reactive conditions and has been observed in patients with TCL.³ Bone marrow biopsy was negative for evidence of disease.

Table 1 Phase II Trial of Romidepsin in Patients With Peripheral T-Cell Lymphoma: Cycle 1 Toxicity

	Number of Patients (%) (n = 39)			
	Grade 1	Grade 2	Grade 3	Grade 4
Thrombocytopenia	28%	5%	13%	0
Granulocytopenia	5%	13%	13%	8%
Nausea	49%	8%	3%	0
Fatigue	33%	5%	10%	0
Vomiting	13%	8%	3%	0
Anorexia	18%	5%	0	0
Dysgeusia	5%	3%	0	0
Headache	15%	3%	0	0
Hypophosphatemia	0	0	3%	0
Hyperuricemia	0	0	0	3%

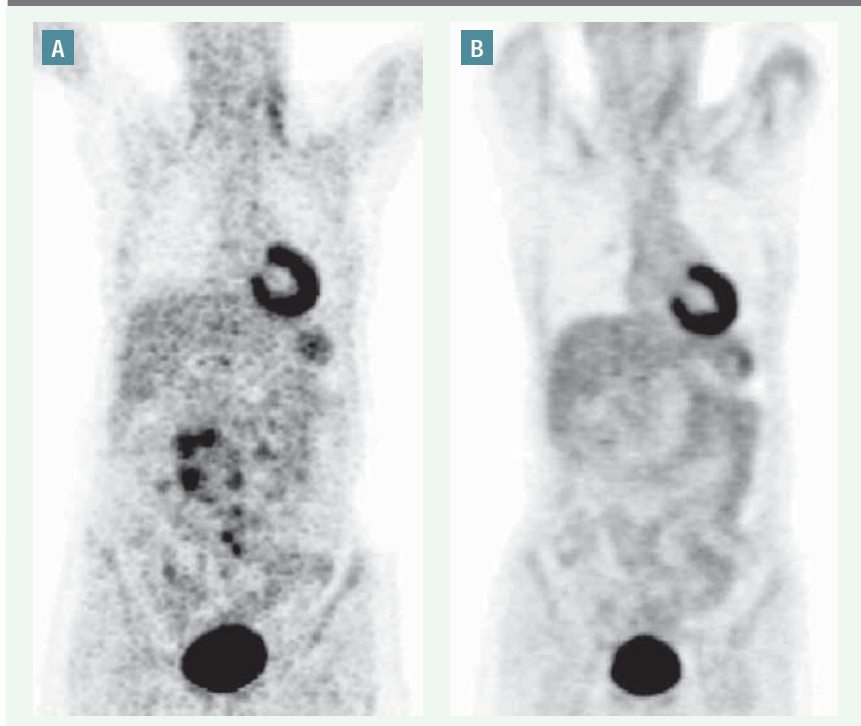
Romidepsin was administered at a starting dose of 14 mg/m² I.V. over 4 hours on days 1, 8, and 15 every 4 weeks.¹ While dose adjustments could be made for significant granulocytopenia or thrombocytopenia, the patient completed 13 cycles (39 doses) and had only 1 dose reduction due to a platelet count of $69 \times 10^9/L$, which was slightly below the cutoff of $75 \times 10^9/L$. The side effects observed in the patient were similar to those observed in other patients treated with romidepsin, which appear to be a class effect in patients treated with histone deacetylase inhibitors (HDACIs).⁴ Common adverse events noted in cycle 1 in all 39 patients with PTCL treated on the protocol included thrombocytopenia, granulocytopenia, nausea, and fatigue (Table 1).¹

The patient experienced a significant decrease of her lymphadenopathy with romidepsin, demonstrated best by the PET scan obtained prior to initiating therapy (Figure 1A) and the repeat PET obtained after 8 months of therapy (Figure 1B). However, after 1 year on pro-

This article includes discussion of investigational and/or unlabeled uses of drugs, including the use of romidepsin in peripheral T-cell lymphoma.

Figure 1

Significant Reduction in Lymphadenopathy After Romidepsin Therapy in a Patient With Peripheral T-Cell Lymphoma



Positron emission tomography scans of a patient with peripheral T-cell lymphoma revealing lymphadenopathy prior to romidepsin therapy (A) and reduction in lymphadenopathy after 8 months of romidepsin therapy (B)

tocol, a PET scan revealed evidence of progression, and a CT scan revealed progression of mesenteric lymphadenopathy. The patient had a declining platelet count, and bone marrow biopsy revealed involvement with her lymphoma. Gemcitabine therapy was initiated but was complicated by rash and peripheral edema. The patient received EPOCH (etoposide/prednisone/vincristine/cyclophosphamide/doxorubicin) chemotherapy combined with fludarabine and achieved a good response of short duration.

When the patient was taken off the romidepsin study, she stated that her goal was to be able to dance at her daughter's wedding, scheduled 8 months later. She was able to achieve that goal; however, she died < 6 months after that.

Peripheral T-Cell Lymphoma

The estimated incidence of NHL in the United States in 2008 is approximately 66,000, with an estimated mortality of approximately 19,000.⁵ Although there are many subclassifications, NHLs can generally be divided into those of B-cell origin (approximately 85%), T-cell origin (approximately 10%), and non-B- or T-cell types, such as those of natural killer cell origin (approximately 5%).

In PTCLs, a T-cell receptor gene rearrangement can be detected in a mature, or postthymic, T-cell clone.² These lymphomas are also divided into several subclassifications. While there are specific subtypes based on pathologic phenotype and/or clinical presentation, the largest subtype is PTCL unspecified, which includes PTCLs that do not fit into a specific category. Specific disease entities are associated with the development of TCL and require vigilance; for example, patients with celiac sprue or gluten-sensitive enteropathy are at risk for developing enteropathy-associated TCL.^{2,6}

The role of PET scanning in evaluation, staging, and response to therapy has been well defined in patients with B-cell lymphoma.⁷ While most studies that have evaluated PET in patients with NHL have included only a small number of patients with TCLs,⁸ a few small reports have evaluated the role of PET in patients with TCL.⁹⁻¹¹

Approaches to Therapy

First-line therapy for patients with PTCL is generally considered to be the same as that for patients with B-cell lymphoma.^{2,6} However, patients with PTCL generally experience a shorter duration of response and survival than those with B-cell lymphoma.^{6,12} Some classifications of PTCL, most notably anaplastic lymphoma kinase-positive (ALK⁺) large-cell TCL, do demonstrate a better response to chemotherapy and a better prognosis than other classifications.

One possible explanation of the poorer outcome with PTCL is that there are more effective second-line (and further) therapeutic options for patients with B-cell lymphoma than there are for those with PTCL, which was the case even prior to the introduction of rituximab, indicating that these tumors have a different biology.⁶ Additional agents need to be developed to help patients who relapse or are refractory to therapy and that can be used with first-line therapy to increase the number and duration of responses. Newer agents that have demonstrated activity in patients with PTCL include pentostatin and pralatrexate.^{13,14} While stem cell transplantation has an established role in the treatment of patients with ALK⁺ anaplastic large-cell lymphoma, it is still investigational in patients with PTCL.¹⁵

Many clinically available agents, such as alemtuzumab, bortezomib, gemcitabine, and denileukin diftitox, have demonstrated activity in patients with relapsed/refractory PTCL.

Table 2 Agents for Treatment of Peripheral T-Cell Lymphoma: Efficacy

	Number of Patients	Setting	Number of Patients (%)		
			Overall Response Rate	Complete Response Rate	Partial Response Rate
Alemtuzumab	14	Relapsed/refractory	5 (36%)	3 (21%)	2 (14%)
Bortezomib	2	Relapsed/refractory	1 (50%)	1 (50%)	0
Gemcitabine	8	Relapsed/refractory	5 (63%)	1 (13%)	4 (50%)
Denileukin Diftitox	27	Relapsed/refractory	13 (48%)	6 (22%)	7 (26%)

Enrollment in a clinical trial or use of one of these agents is currently recommended for second-line therapy for these patients by the National Comprehensive Cancer Network Guidelines (Table 2).¹⁶ Alemtuzumab, an anti-CD52 monoclonal antibody, was evaluated in 14 patients with PTCL who had failed 1 or 2 lines of therapy.¹⁷ The overall response rate (ORR) was 36%, with 3 patients achieving a complete response (CR) and 2 achieving a partial response (PR). This pilot phase II study was terminated early due to 5 treatment-related deaths. The proteasome inhibitor bortezomib was evaluated in a phase II study in 12 patients with previously treated TCL, including 2 with PTCL unspecified (PTCLU).¹⁸ One of the patients with PTCLU achieved a CR. No grade 4 hematologic toxicity was reported, and the most common nonhematologic adverse event was grade 1-3 neuropathy in 50% of the patients. In a phase II study of gemcitabine that included 8 patients with relapsed/refractory PTCLU, the ORR was 63%, with 1 patient achieving a CR and 4 patients achieving a PR.¹⁹ Gemcitabine was well tolerated, with no reports of grade 3/4 hematologic adverse events. Denileukin diftitox, an interleukin (IL)-2-cholera toxin conjugate, has demonstrated activity in relapsed/refractory PTCL²⁰ and is now under investigation in combination with CHOP in patients with newly diagnosed PTCL.²¹

Histone Deacetylase Inhibitors

The phase II trial in which the patient described herein was enrolled¹ was initiated as a result of the responses observed in the initial phase I trial of romidepsin in a patient with PTCL unspecified and patients with cutaneous TCL (CTCL).²²

The HDACIs represent a new class of antineoplastic agents that include compounds traditionally studied as differentiating agents, such as sodium butyrate.⁴ These agents induce cell-cycle arrest, differentiation, and apoptosis in tissue culture and xenograft models. This is thought to occur, at least partially, through regulation of the expression of genes involved in cell-cycle regulation

Table 3 Phase II Trial of Romidepsin in Patients With Peripheral T-Cell Lymphoma: Efficacy

	Number of Patients (%) (n = 39)	Median Duration of Response (Range)
Complete Response	3 (7%)	12 (9-43+) months
Partial Response	8 (21%)	12 (2-38+) months
Stable Disease	5 (13%)	6 (4-8+) months
Progressive Disease	18 (46%)	NA
Not Evaluable	5 (13%)	NA

Abbreviation: NA = not applicable

Romidepsin is a bicyclic depsipeptide that is a fermentation product of *Chromobacterium violaceum* and a potent inhibitor of HDAC activity. Following responses observed in the phase I trial conducted at the NCI in patients with CTCL and PTCL,²² we opened a phase II trial of romidepsin in patients with these lymphomas.¹ The trial is now multi-institutional.

The major toxicities that have been associated with administration of romidepsin are nausea, vomiting, taste changes, and fatigue.^{1,23} While neutropenia and thrombocytopenia are observed, they are characterized by rapid onset and resolution.

An update on the 39 patients with PTCL treated in this multi-institutional phase II trial has been presented.¹ The ORR was 28%, with 3 patients (7%) demonstrating evidence of complete and durable responses (Table 3). This trial of single-agent romidepsin represents a promising start and suggests that this agent, as well as other HDACIs, should undergo further clinical evaluation in patients with PTCL.

As with the development of all new classes of antineoplastic agents, there are many questions that can be evaluated, including the underlying mechanisms of response or resistance to these agents, predictors of response, and ways to increase response, leading to the evaluation of agents that might be used in combination with HDACIs.²⁴ Preclinical studies are ongoing to determine what agents might have increased efficacy when combined with an HDACI. One focus of study is the effect of an HDACI on the expression of the targets of other antineoplastic agents, including the IL-2 receptor CD25 and the retinoic acid receptor. In the laboratory, increased expression of these receptors has been found following treatment with romidepsin or other HDACIs. This strategy could lead to combining an HDACI with agents such as the anti-Tac antibody or retinoids. There is

precedent for an interaction between retinoid responsiveness and HDAC inhibition; in a patient with acute promyelocytic leukemia who was resistant to retinoic acid, Dr. Warrell and colleagues were able to demonstrate a resensitization to retinoic acid after treatment with phenylbutyrate.²⁵

Conclusion

The patient described herein had recurrent PTCL following CHOP and radiation therapy, presented with extensive lymphadenopathy, and was enrolled in a phase II trial of romidepsin.¹ Treatment with romidepsin resulted in a significant reduction in the lymphadenopathy 8 months after the initiation of therapy. However, the patient progressed after 1 year on the protocol and was taken off study. Treatment of PTCL is challenging because tumors display intrinsic chemoresistance and no standard second-line therapy exists. The HDACIs, including romidepsin, represent novel and effective treatment options for patients with PTCL. Additional study is needed to fully evaluate their therapeutic potential in PTCL.

Note from the publisher: The case report described herein represents a single-patient experience. The outcomes seen in individual cases can vary.

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 - a. Granulocytopenia, thrombocytopenia, and nausea
 - b. Granulocytopenia, thrombocytopenia, and fatigue
 - c. Granulocytopenia, hypophosphatemia, and anorexia
 - d. Thrombocytopenia, vomiting, and dysgeusia
2. Which of the following treatment options is recommended by the National Comprehensive Cancer Network for patients with relapsed/refractory PTCL?
 - a. Clinical trial
 - b. Denileukin diftitox
 - c. Alemtuzumab
 - d. Gemcitabine
 - e. All the above
3. Which of the following statements regarding efficacy results from a phase II trial of romidepsin in patients with relapsed/refractory PTCL is TRUE?
 - a. The median duration of response was 12 months (range, 2-43+ months).
 - b. A complete response was achieved by > 10% of the patients.
 - c. A response was achieved by almost 30% of the patients.
 - d. a and c
 - e. b and c

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