

Clinical Roundtable Monograph

HDAC Inhibitors: Mechanisms of Action and Efficacy in the Treatment of Hematologic Malignancies

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Abstract

The identification of the cellular and molecular mechanisms of malignant transformation has allowed for the development of targeted anticancer therapies with increased efficacy and fewer adverse effects. A novel target for the treatment of hematologic malignancies is histone deacetylase (HDAC), which regulates gene transcription, producing disparate effects on cell growth and survival. Indeed, studies have already demonstrated that cell-specific mechanisms result in increased HDAC activity in various types of hematologic malignancies. HDAC inhibitors reduce proliferation and promote differentiation of many cancer cell types in vitro. Phase I and II studies with several HDAC inhibitors, including suberoylanilide hydroxamic acid (SAHA), depsipeptide, plitidepsin, and PXD101, have already demonstrated improved outcomes in patients with various types of relapsed or refractory hematologic malignancies. Further, these agents appear to be well tolerated, with the most frequent adverse effects being fatigue, nausea, diarrhea, and thrombocytopenia. Because the majority of these studies were performed in patients with refractory or relapsed disease, it is possible that HDAC inhibitors may have even greater efficacy in those patients who have not been heavily pretreated. Further study of the use of HDAC inhibitors in combination with other agents is expected.

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HDAC Inhibition: Mechanisms of Action



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Introduction

New cases of hematologic malignancies, including leukemia, lymphoma, and myeloma, account for 9% of cancer cases diagnosed in the United States. While refinements in conventional chemotherapy regimens have resulted in better outcomes and decreased toxicity, approximately 60,000 persons still die of hematologic malignancies each year.¹ Over the past two decades, an increased understanding of the biochemical and molecular mechanisms that result in malignant transformation have led to the identification of novel therapeutic targets on the cellular and molecular levels. Indeed, recent success with monoclonal antibodies and small molecule inhibitors directed against specific signal transduction elements has demonstrated that targeted therapy can further improve outcomes while simultaneously reducing systemic toxicity.

This discussion will provide an overview of the role of the novel therapeutic target histone deacetylase (HDAC) in the regulation of cellular transcription and tumorigenesis as well as the mechanisms by which HDAC inhibitors may interfere with malignant cell growth in the context of hematologic malignancies.

Normal Physiologic Function of HDAC

Aberrant regulation of gene transcription can contribute to tumorigenesis, either by increasing expression of growth-promoting elements or by suppressing expression of elements that are required to initiate the host antitumor response (eg, a tumor suppressor gene product).² One of the mechanisms by which transcriptional activity is regulated in eukaryotic cells is via the structural organization of DNA. Specifically, eukaryotic DNA is compartmentalized in the nucleus in the form of chromatin, a highly organized and dynamic macromolecular complex that consists of DNA wrapped around an octamer composed of several histone proteins (H2A, H2B, H3, and H4). Posttranslational modification of the N-terminal positively charged lysine-rich tails of the histones occurs via several different mechanisms, including acetylation, methylation, phosphorylation, and ubiquitination.³

The acetylation of the histone tails is regulated by a balance between the antagonistic activities of histone acetyl-transferases (HATs) and HDACs. HATs acetylate the

histone lysine tails, resulting in the opening of the chromatin (euchromatic) away from the core protein octamer and thereby promoting gene transcription by allowing transcription factors access to the DNA promoter regions. By contrast, HDACs remove acetyl groups from the histone lysine tails, leading to condensation of the DNA around the core proteins and subsequent inactivation of gene transcription.² As a result of their ability to modulate transcription of diverse cellular elements, HDAC proteins can act as upstream regulators of fundamental cellular processes, including cell cycle control, differentiation, and apoptosis.³

At least 17 human genes that encode putative HDACs have been described, which have subsequently been categorized into three different families.⁴ The class I HDACs are related to the yeast transcriptional regulator RPD3, while the class II HDACs are homologous to the yeast deacetylase HDAC1. The class III HDACs, also known as SIRT1, are NAD⁺-dependent enzymes with homology to the yeast transcriptional repressor Sir2.

HDAC and Cancer

If enzymes mediating histone acetylation are important for normal cellular function, then abnormal activity of HDACs may be associated with tumorigenesis. Indeed, increased HDAC activity is associated with modulation of cellular oncogenes and tumor suppressor gene expression and can be associated with the subsequent development of specific forms of leukemia and lymphoma.⁴

Studies have demonstrated various mechanisms by which oncogenic proteins can interact with HDACs. For example, overactivity of the *ras* oncogene, a common mutation found in cancer cells, may lead to the phosphorylation and subsequent nuclear localization of HDACs, leading to altered transcription.⁵ Other investigators have demonstrated that the AML1-ETO and TEL-AML1 fusion proteins promote the development of acute myeloid leukemia (AML) and acute lymphoblastic leukemia through the recruitment of HDACs.⁶ Furthermore, in the context of acute promyelocytic leukemia (APL), fusion proteins between the retinoic acid receptor (RAR) transcription factors and other genes have high affinities for HDACs and result in the suppression of RAR-targeted gene transcription even in the presence of retinoids.⁷

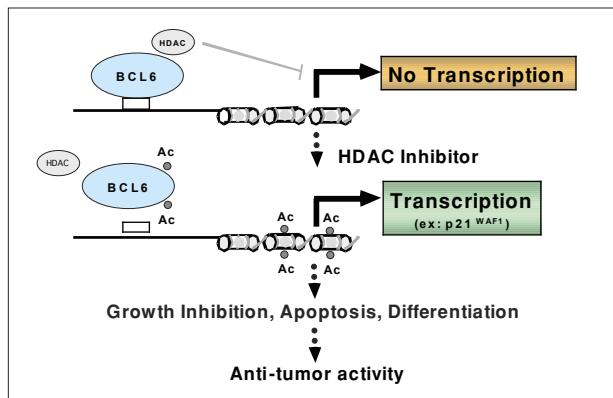


Figure 1. BCL6 is constitutively expressed in a large proportion of B-cell lymphomas and is involved in the suppression of genes involved in the control of lymphocyte activation, differentiation, and apoptosis. In the acetylated state, BCL6 is inactive and loses its ability to repress transcription and to induce cell transformation. Pharmacological inhibition of histone deacetylase (HDAC) with agents such as vorinostat may result in the accumulation of acetylated BCL-6, expression of the cell-cycle regulator p21^{WAF1} and ultimately growth inhibition, apoptosis, and differentiation of B-cell lymphoma cells.

HDACs can also play a critical role in the pathogenesis of other types of lymphoma, including diffuse B-cell lymphoma. Studies have demonstrated that overexpression of the transcriptional repressor LAZ3/BCL6 leads to recruitment of HDACs in patients with certain forms of non-Hodgkin lymphoma. Deacetylation of BCL6 by HDAC upregulates its ability to suppress genes involved in lymphocyte activation, differentiation, cell cycle arrest, and apoptosis (Figure 1).⁸

HDAC Inhibition and Hematologic Malignancies

HDAC inhibitors bind to the catalytic pocket of the HDAC enzyme, with the long aliphatic chain inserting into the pocket while the polar hydroxamate group chelates the zinc ion required for catalysis.³ Experiments have demonstrated that HDAC inhibitors induce cell cycle arrest in mammalian cells at both G1 and G2 phases, induce terminal differentiation of murine erythroleukemia cells, and induce apoptosis in neural, lymphoid, and colorectal cancer cell lines.² The subsequent development of a variety of compounds that inhibit HDAC activity has facilitated the investigation of the disparate mechanisms by which HDAC inhibitors exert their anticancer effects in individual cell types.

Studies have demonstrated that nearly all types of HDAC inhibitors can upregulate the cyclin-dependent kinase inhibitor p21^{WAF1/CIP1} and thereby block proliferation in a variety of tumor cell types.⁹ Other studies suggest that HDAC inhibitors exert cell-specific antitumor effects in a variety of hematologic malignancies. For example, in

multiple myeloma cell lines, treatment with HDAC inhibitors resulted in increased levels of p21^{WAF1/CIP1}, p53, and unphosphorylated retinoblastoma protein and a reduction in expression of various antiapoptotic genes, including *bcl2*, *bcl-xl*, and *mcl-1*.¹⁰ Additionally, HDAC inhibitors abrogate the transcriptional repressor capacity of *bcl6* in lymphoma cell types, resulting in the transcription of genes that promote differentiation. They have also been shown to block fusion protein-mediated increases in HDAC activity in APL cells, thereby promoting differentiation.⁸ The mechanistic efficacy of HDAC inhibitors is supported by reports of a patient with cutaneous T-cell lymphoma (CTCL) who experienced a partial response after HDAC inhibitor treatment; biopsy specimens from this patient were notable for the presence of hyperacetylated histones.¹¹

Conclusions

Many lines of preclinical and clinical data suggest that the acetylation state of core DNA histones is a common molecular target through which HDACs may regulate the transcription of disparate cellular elements that mediate growth and survival. Mechanisms of HDAC inhibitor-mediated antitumor effects may be cell-specific in a variety of hematologic malignancies. These findings provide a rationale for the treatment of tumors with HDAC inhibitors. Further study to characterize the precise changes in transcriptional activity by which HDAC inhibitors exert their antineoplastic effects will continue to provide new insights into the underlying pathobiology of cancer, and hopefully provide a new therapeutic rationale for the treatment of patients.

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Phase I and II Trials of HDAC Inhibitors in Hematologic Malignancies



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Introduction

Increases in HDAC activity can alter transcription of various signal transduction elements involved in cellular growth and survival and thereby promote tumorigenesis.¹ The present discussion will briefly review phase I and II data regarding the efficacy and toxicity of various HDAC inhibitors, including suberoylanilide hydroxamic acid (SAHA), depsipeptide, plitidepsin, and PXD101, in the context of hematologic malignancies.

SAHA

Gore and colleagues² demonstrated a correlation between higher levels of histone 2B acetylation in CD34+ cells and survival in patients with AML and concluded that such patients may benefit from therapy that modifies histone deacetylation.

SAHA, also known as vorinostat (Merck), is an oral HDAC inhibitor that modulates acetylation of histones and promotes apoptosis and differentiation of various leukemic cell lines in vitro. Heany and colleagues³ performed a dose escalation phase I trial of vorinostat in 29 patients with heavily pretreated aggressive non-Hodgkin lymphoma or Hodgkin disease and in 4 other patients with multiple myeloma, peripheral T-cell lymphoma (PTCL), AML, or myelodysplastic syndrome (MDS). Reduction in measurable tumor volume was observed in 6 patients, including 1 patient with transformed B-cell lymphoma who had a complete remission. In addition, a patient with diffuse large B-cell lymphoma (DLBCL) who had relapsed after a stem cell transplant experienced a partial remission, and a patient with refractory Hodgkin's disease had stable disease for 9 months. Major toxicities included fatigue, diarrhea, anorexia, dehydration, and myelosuppression. Of note, thrombocytopenia resolved quickly after the vorinostat course was complete.

Subsequently, Garcia-Manero and colleagues⁴ conducted a phase I study of vorinostat (100 mg three times daily for 14 consecutive days every 21 days) with dose escalation in 50 mg increments in 15 patients with leukemia or MDS. At the lowest dose, 1 patient with AML experienced

improvement in blast counts but subsequently progressed. At the intermediate dose level, 1 patient with chronic lymphocytic leukemia (CLL) experienced a marked decrease in lymphadenopathy. At the highest dose, an elderly patient with AML had a complete remission after two cycles of therapy, and 2 other patients with AML and 1 patient with MDS had a decrease in marrow blasts. The investigators concluded that the recommended dose in a phase II setting in this population was 250 mg three times daily for 14 days every 21 days. Major toxicities seen in this trial included nausea, vomiting, and fatigue, all of which resolved when the medication was discontinued. Further, none of the patients developed significant thrombocytopenia.

Duvic and colleagues⁵ reported impressive results from a phase II study of three different dose schedules of vorinostat (300 mg bid for 3–5 d/wk; 300 mg bid for 14 d and then 200 mg bid; or 400 mg daily) in 27 patients with advanced CTCL. Ten of 27 patients experienced partial remissions. Further, there was a demonstrable decrease in lymphadenopathy in 15 patients, with response durations of 13–16 weeks. Of note, response rates were greatest for those who received the highest dose of vorinostat, but these patients also had higher rates of toxicities. The most common reported toxicities in this study were fatigue (73%), diarrhea (57%), and mild-to-moderate thrombocytopenia (57%).

Depsipeptide and Plitidepsin

Another agent that has been studied in clinical trials is depsipeptide (Gloucester Pharmaceuticals), an intravenous HDAC inhibitor. Piekarz and colleagues⁶ conducted a multi-institutional phase II trial of depsipeptide (4-hour infusion of 14 mg/m² on days 1, 8, and 15 of a 28-day cycle) in patients with heavily pretreated CTCL, PTCL, or other mature T-cell lymphomas. Patients with Sézary syndrome all responded, with 3 of 8 having a complete response and the other 5 having a partial response. The response duration in these patients was 18 months. Other patients showed stabilization of their disease lasting 6 months. Further, clinical response correlated with the degree of histone H3 acetylation that was measured in patient samples obtained

four hours after initiation of the depsipeptide infusion. Toxicities included nonspecific ST-T wave changes on electrocardiograms, but there was no significant change in cardiac function as assessed by echocardiograms, multiple-gated acquisition scans, and troponin assays. Further, patients who received multiple courses of depsipeptide showed no signs of cumulative toxicity.

Subgroup analysis of a cohort of patients with advanced PTCL treated on this trial was subsequently reported.⁷ Of 17 patients with PTCL, four (24%) had a partial response to therapy, and these responses lasted 9 and 12 months in 2 patients and 4 months in the other 2 patients. Further, the drug was well tolerated by this population of patients. ST-T wave changes were again noted without significant cardiac dysfunction. In fact, the overall toxicity profile for depsipeptide was similar to that of vorinostat, with nausea, fatigue, diarrhea, and thrombocytopenia being the major toxicities.

Niesvizky and colleagues⁸ performed a multicenter phase II trial of depsipeptide (4-hour infusion of 13 mg/m² on days 1, 8, and 15 of a 28-day cycle) in 12 patients with relapsed or refractory multiple myeloma. The investigator reported that 11 of the 12 patients had stable disease, as measured by serum protein electrophoresis or light-chain measurement. After receiving two cycles of therapy, 2 patients had stable disease on ongoing therapy. Further, 5 of the 11 patients discontinued with stable disease, and 4 patients progressed after completing one to two cycles of therapy. The major toxicities were thrombocytopenia, which was reported in two patients and necessitated dose reduction, and ST-segment depression, which was significant in only one patient.

Plitidepsin (Aplidin, PharmaMar) is a cyclic derivative of depsipeptide that has shown activity similar to depsipeptide in multiple cell lines. Mateos and colleagues⁹ performed a multicenter phase II trial of plitidepsin (3-hour infusion of 5 mg/m² every 2 weeks) in 13 patients with refractory or relapsed multiple myeloma. The median number of cycles received was four. One patient achieved a partial response, with a 70% reduction in the M-protein that lasted for 8 months. Stable disease was observed in 3 patients, and lasted up to 2 months in 1 patient. Toxicities included fatigue, myalgias, and transient transaminase elevations. Further, 2 patients developed thrombocytopenia.

PXD101

PXD101 (CuraGen/TopoTarget A/S) is a potent HDAC inhibitor, with deacetylating efficacy observed even when used in nanomolar concentrations. This agent has been studied *in vitro* and has been shown to inhibit the growth of a number of different tumors, including hematopoietic and solid tumors.

Gimsing and colleagues¹⁰ performed a phase I study of PXD101 (30-minute infusion of 600 or 900 mg/m²/d on days 1–5 of a 21-day cycle) in 11 patients with various hematologic malignancies. To date, stable disease has been achieved in 1 patient with multiple myeloma and 1 patient with CLL. The adverse events related to therapy include nausea, fatigue, and potential tumor lysis syndrome in 1 patient with multiple myeloma. This agent is currently being explored in phase II trials in patients with CTCL and PTCL.

Conclusions

Data from phase I and II studies suggest that HDAC inhibitors have clinical efficacy in patients with a variety of hematologic malignancies, even in those with refractory or relapsed disease. Further, these agents have a favorable safety profile. Because the majority of these studies were performed in patients with refractory or relapsed disease, it is possible that HDAC inhibitors may have even greater efficacy in those patients who have not been heavily pretreated.

Areas for future investigation include evaluation of the efficacy of HDAC inhibitors in combination with conventional and targeted chemotherapies as well as the ability of gene profile analysis studies to predict which patients may respond to HDAC inhibitor therapy.

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Question and Answer Forum

Drs. O'Connor and Foss answer further questions about HDAC inhibition and its application in the treatment of hematologic malignancies.

Do HDAC inhibitors have particular application in hematologic malignancies?

Dr. Owen O'Connor There are some cell-specific mechanisms involving HDAC that have been demonstrated in various hematologic malignancies. Dysregulation of *bcl6* in patients with B-cell lymphoma may provide one mechanistic rationale for the use of HDAC inhibitors in these diseases. Likewise, the accumulation of key cell cycle-dependent kinase inhibitors and other critical regulators of cell growth and survival following their transcriptional activation provides yet another explanation for the multiple effects these types of drugs can have on cancer cell biology

Dr. Francine Foss There are some characteristics of HDAC inhibitors that fill a niche in the treatment of hematologic malignancies. Certainly, the availability of the oral agent vorinostat is promising for ambulatory treatment and for maintenance therapy. The fact that HDAC inhibitors have relatively low immunosuppression toxicities is very valuable for a patient population that is already immunosuppressed by the nature of their disease. Finally, HDAC inhibitors may be particularly valuable for patients with aggressive CTCL or PTCL who often relapse after systemic chemotherapy and in whom impaired performance status often limits the use of more aggressive therapies such as autologous or allogeneic stem cell transplantation.

Can you explain the association between HDAC inhibitors and thrombocytopenia?

FF It's not really known why thrombocytopenia occurs with these agents, but it seems to be a common pattern if one looks at all of the different HDAC inhibitors. The good news is that the incidence of significant thrombocytopenia requiring dose modification of HDAC inhibitors is relatively low. In most cases, the thrombocytopenia is mild and managed by holding doses or lowering the dose of the drug. So thrombocytopenia seems to be a much less important toxicity in these patients when compared with the high incidence of fatigue and constitutional symptoms.

OO The nature of the thrombocytopenia seems to be quite unusual compared to other common antineoplastic agents. In this setting, thrombocytopenia is typically very short lived, and evaluation of the bone marrow at the time of the platelet nadir shows very dysplastic megakaryocytes. This is interesting and distinctively different from other anticancer

drugs, which tend to be more nonspecific, generally producing a marked depletion in the megakaryocyte population. While many theories have been advanced to explain these observations, most have focused on the ability of HDAC inhibitors to facilitate an impairment in the terminal budding of platelet production, which explains the observation that once you stop treatment platelet counts typically recover rapidly and uneventfully.

What do you envision in terms of combination therapy incorporating HDAC inhibitors?

FF The two logical combinations in terms of mechanisms of action include the use of HDAC inhibitors, which are agents that modulate gene transcription, with agents like bortezomib (Velcade, Millennium Pharmaceuticals), which affect protein synthesis—the idea being that there could be a synergistic reaction between the two. Some in vitro data have demonstrated that synergy. Combining HDAC inhibitors with hypomethylating agents is also being explored.

OO The future development of HDAC inhibitors in combination with more traditional forms of chemotherapy will likely be driven by empirical observations made in preclinical experiments. A priori, there is no real rationale for why certain classes of antineoplastic agents might be synergistic with these drugs, though many have postulated that dual targeting of various epigenetic pathways with HDAC inhibitors and hypomethylating agents like decitabine could be complementary. I think a more crucial question to answer relates to the importance of any schedule dependency with these agents and other classic cytotoxic drugs. Given the plethora of different biologic effects the HDAC inhibitors have, empirically understanding the importance of schedule will be crucial as we begin to translate laboratory findings into novel clinical trials.

Are the clinical studies of HDAC inhibitors relatively small because they are still at phase II or because they are for rare diseases?

FF These diseases are rare, and it's difficult to accrue 100 patients to a clinical trial. Based on the fact that these are rare diseases, the US Food and Drug Administration will often times approve a drug based on several phase II studies as opposed to a randomized phase III trial. I believe that these agents could receive regulatory approval under orphan drug status.

