Brief Review of Vorinostat

Colin McGuire and Jin Lee
University of Pittsburgh Medical Center, Arnold Palmer Pavilion at Mountain View Medical Park, Greensburg, PA 15601, USA. Email: leejs@upmc.edu

Abstract: The histone tails of histone octamers play an intricate role in transcription, and aid the histone interaction and binding with the negatively charged DNA phosphate backbone. Histone acetyl transferases and histone deacetylase inhibitors respectively accomplish acetylation and deacetylation of the lysine residue of the histone tail. Vorinostat is the first and only histone deacetylase inhibitor with activity in cutaneous T-cell lymphoma (CTCL) approved by the US Food and Drug Administration (FDA). CTCL refers to a diverse group of disorders, including the most common mycosis fungoides, and the less common but more aggressive Sézary syndrome. The exact mechanism of action of vorinostat is unknown; however, it involves the up- and down-regulation of multiple cell cycle pathways. Vorinostat exhibits better efficacy in hematologic malignancies than in solid tumors. Numerous clinical trials involving vorinostat alone and in combination with other agents in multiple malignancies and solid tumors have reported patient clinical benefit. Overall, the adverse-effect profile of vorinostat is very favorable, and the product is a good candidate for single-agent use as well as for combination therapy.

Keywords: vorinostat, epigenetic, HDAC inhibitor, CTCL
Introduction

The basic packing unit of chromatin is the nucleosome, consisting of a DNA double helix wrapped around a core of 8 histone proteins known as an octamer. Histone tails normally have a positive charge, which helps the histone interact with and bind to the negatively charged phosphate groups on the DNA backbone. Acetylation neutralizes the positive charge on the histone tail and allows transcription to take place while the chromatin is expanded. Histone deacetylation involves the removal of the acetyl groups of the lysine residues on the histone tails, thus increasing the affinity of histone octamers for the DNA wrapped around them. This leads to a tightened chromatin structure, which represses DNA transcription.

This system of acetylation and deacetylation is regulated by two types of enzymes, histone acetyl transferases and histone deacetylases (HDACs). In several malignancies like leukemia and lymphoma, as well as stomach, prostate and colon cancer, the decreased acetylation of the histone is associated with loss of functional gene expression of several tumor suppressors and/or cell cycle regulatory proteins. This loss affects growth arrest and proliferation as well as differentiation and apoptosis.

The HDACs involve 18 genes which are subdivided into two families and four classes, differing from each other in terms of their structure and biological activity. The classical family which is the primary target of HDAC inhibitors (HDACis) consists of class I (HDAC1, 2, 3, and 8), class IIa (class IIa, comprising HDAC4, 5, 7, and 9; and class IIb, comprising HDAC6 and 10), and class IV (HDAC11). The class III HDACs (SIRT 1–7) consist of the sirtuin family and are structurally unrelated to classical HDACs. The HDACis can also be subdivided by their structural differences. They include the short chain fatty acids butyrate and valproic acid; the hydroxamates which include trichostatin A, vorinostat, LBH589 (panobinostat), PXD101 (belinostat), oxamflatin, and tubacin; the benzamides which include SN275 and MGCD0103; and the cyclic tetrapeptides which consist of trapoxin A, FK228 (romidepsin), and apicidin. The hydroxamates are the only pan-HDACi with the ability to target all classical HDACs.

This discussion will focus primarily on vorinostat (suberoylanilide hydroxamic acid), the first and only HDACi currently approved for clinical use by the United States Food and Drug Administration (US FDA). Vorinostat has a diverse activity in many cancer types, both solid (ovarian cancer cells and xenografts, colon cancer cells, breast cancer, lung cancer, and hematologic malignancies). However, there is more evidence of vorinostat efficacy in hematologic malignancies than in solid tumors.

Clinical Significance

Vorinostat approved indication is for the treatment of cutaneous manifestations in patients with CTCL who have progressive, persistent, or recurrent disease on or following two systemic therapies. CTCL refers to a diverse group of lymphoproliferative disorders characterized by infiltration of the skin by neoplastic T-cells. According to the latest Surveillance, Epidemiology and End Results (SEER), CTCL now comprises approximately 3.4% of all non-Hodgkin’s lymphoma. Mycosis fungoides (MF) is the most common form of CTCL, accounting for approximately 44% of all CTCL. Whereas MF is an indolent disease involving the skin and eventually other extranodal areas, Sézary syndrome, which accounts for 1.5% of CTCL cases, is a more aggressive leukemic variant with a significant number of circulating malignant T-cells. The treatment of CTCL is dependent upon both the disease stage and previous treatment response. Generally, if the patient has skin involvement in the form of patches or plaques without extracutaneous disease, the treatment is limited to skin-directed therapy. Systemic treatment is recommended for patients with more advanced disease and those who are refractory or have developed dose-limiting toxicities to the skin-directed therapies. There are several systemic treatments including cytokines (interleukin alpha), bexarotene (a retinoid), denileukin diftitox (ONTAK), cytotoxic chemotherapy, hematopoietic stem cell transplant, and the new epigenetic modulator, vorinostat. The term epigenetic refers to a change in gene expression caused by mechanisms other than changes in the underlying DNA sequence. Irregularities in cellular epigenetics have been implicated in the development of several malignancies. Currently, there are three FDA-approved epigenetic agents for oncology: azacitidine (Vidaza, Celgene), 5-aza-2’deoxyctydine (Dacogen, Eisai), and vorinostat (Zolinza®, Merck). Azacitidine and 5-aza-2’deoxyctydine are DNA hypomethylating agents and are FDA-approved for...
the treatment of myelodysplastic syndrome, whereas vorinostat is an HDACi approved for the treatment of CTCL. A wealth of preclinical in vivo and in vitro data has been reported for vorinostat alone and in combination. A Phase I trial demonstrated efficacy in both solid and hematologic malignancies, and both the intravenous (IV) and oral formulations were well tolerated. However, the IV formulation had a higher rate of thrombocytopenia and myelosuppression than the oral formulation which tended to have greater gastrointestinal side effects. Two Phase II trials were conducted based upon the Phase I data. In a dose-ranging Phase IIa study, 33 patients with CTCL who had received a median of five prior therapies were assigned to receive vorinostat 200–400 mg on varying dosing schedules (Group 1, 400 mg daily, n = 13; Group 2, 300 mg twice daily for 3 days with 4-days rest, n = 11; Group 3, 300 mg twice daily for 14 days with 7-days rest followed by 200 mg twice daily, n = 9). An overall response rate of 24% was observed for all patients (31% for Group 1 patients) with a median time to progression of 30.2 weeks observed in the responders. Time to response was reported as 11.9 weeks with relief in pruritus seen in 14 out of 31 evaluable patients. Vorinostat was of clinical benefit (pruritus relief and/or stable disease) to 58% of the study patients. The second trial was an open-labeled, Phase IIb multicenter study of 400 mg daily oral vorinostat in 74 patients with advanced and refractory CTCL, who had received at least two prior systemic therapies, at least one of which was bexarotene (unless intolerable). The overall response rate was 30%, the median time to response was 56 days, and the median duration of response and time to progression were estimated to be >185 days and >9.8 months, respectively. One patient who achieved an objective response noted macular/patch lesion enlargement on dose reduction (300 mg) and a new papular component to lesions when therapy ceased for two weeks; however, the lesions responded after dose escalation (400 mg) and the papular component resolved on restarting therapy while patch lesions persisted. These observations suggest that the aggressive tumor component of the neoplastic clone continues to be suppressed by vorinostat, but the more indolent patch component is no longer responsive. Overall, 30% of patients had pruritus relief, and 41.7% of patients with lymph-node involvement experienced shrinkage. Based upon the results of the above studies, vorinostat was approved by the US FDA for treatment of CTCL, becoming the first epigenetic drug to be approved for the disease outside of myelodysplastic syndrome.

Safety Profile
From the two Phase II studies, the most common grade-3 or -4 toxicities noted for vorinostat were thrombocytopenia, fatigue, and dehydration. However, the most common toxicities (all grades) were fatigue, thrombocytopenia, diarrhea, and nausea. Other hematologic adverse effects included anemia and neutropenia, most of which were grade 1 and 2. There was a 5% incidence of pulmonary emboli in the Phase IIb clinical trial but overall the treatments were very well tolerated. In this Phase IIb trial, 11 people required dose modification and 9 patients discontinued due to adverse events. Asymptomatic prolongation of QT interval corrected for heart rate (QTc) was noted in serial electrocardiography in 4% of the patients. Vorinostat was noted to cause fetal harm in animals and consequently carries a Category D status for use in pregnancy.

Mechanism of Action and Resistance
Despite their HDAC class target differences, the exact mechanism of action of HDACis is not fully understood. Their immediate action on the deacetylation of lysine residue of the histone tail is part of their activity and leads to a multitude of effects on cancer cells that encourage cell cycle arrest, differentiation, or apoptosis. It has been reported that HDACi treatment alters between 2%–22% of gene expression with both up- as well as down-regulation. One of these up-regulated genes is CDKN1A, an encoder of protein p21 which specifically inhibits the G1/S transition of the cell cycle. Furthermore, acetylation of the non-histone proteins such as p53, HIF-alpha, pRb, STAT-3, Rel A/p65, or estrogen receptors may impair the HDACi function and promote either cell growth or survival. In addition, acetylation of heat shock protein (HSP) 90 disrupts the chaperone function of HSP90, promoting degradation of pro-growth and pro-survival of the chaperone client protein. HDACis also possess antiangiogenic properties via repression of the vascular endothelial growth factor as well as impairment of HIF-1 alpha stability. HDACis also inhibit the expression of matrix metalloproteinase enzymes.
which degrade the basement membrane surrounding the tumors, an important initial step in metastasis. Direct activation of the apoptotic pathway (intrinsic pathway) is also seen with the HDACi group via increased expression of the pro-apoptotic Bax and BH3 only proteins Bid or Bim.\textsuperscript{3,6} Tumor necrosis factor-related apoptosis induced ligand and FAS system are sensitized by HDACis, leading to an increase in apoptotic response (extrinsic pathway).\textsuperscript{5,6} The efficacy of vorinostat in hematologic malignancies, especially CTCL, and less so in solid tumors suggests that a selective pathway exists which has yet to be elucidated.

A resistance mechanism has been noted and observed, with overexpression of retinoic acid receptor alpha (RAR-alpha) and of preferentially expressed antigen to melanoma (PRAME) which encodes a tumor antigen repressing retinoic acid (RA) signaling. This over-expression of RAR alpha and PRAME-restores repression of RA target genes, allowing cells to overcome proliferation, arrest, and caspase-dependent apoptosis.\textsuperscript{8} In addition, nuclear accumulation of STAT1 and high levels of nuclear pSTAT3 in malignant T-cells have been seen to correlate with lack of response to vorinostat. Other potential means of vorinostat resistance have been noted involving overexpression of the antiapoptotic proteins Bcl-2 or Bcl-XL or deletion of the pro-apoptotic BH3-only proteins Bim and Bid.\textsuperscript{3,4}

**Vorinostat in Combination Therapy**

To date, HDACis have shown synergism with many anti-cancer agents, including cytotoxic agents such as gemcitabine, paclitaxel, cisplatin, etoposide, and doxorubicin as well as mechanism-based agents, including HSP90 inhibitor 17AAG, the proteosome inhibitor bortezomib, and the DNA methylation inhibitor 5’azacytidine.\textsuperscript{7} Currently, there are over 40 ongoing clinical trials with vorinostat, including Phase I, II, and III trials (www.clinicaltrials.gov). Several of these trials target solid tumors and involve combinations of vorinostat with other targeted therapies or with chemotherapeutic agents. Of interest in CTCL is the synergism with retinoic acid and all-trans retinoic acid (ATRA). The RA signaling is enhanced with vorinostat, and combining treatment with RA will augment the RA effects with improved outcome. A study by Steinhoff et al demonstrated feasibility as well as improved efficacy for bexaratene in combination with vorinostat.\textsuperscript{3,6,37} In addition, these trials demonstrated the efficacy of vorinostat in multiple malignancies, as well as the lack of response with myeloma, head and neck cancer, breast cancer, thyroid cancer, and other malignancies.\textsuperscript{4}

**Conclusion**

CTCL is a heterogeneous disease with many features and characteristics. MF and Sézary syndrome constitute the majority of the CTCL cases and vorinostat is a new and capable drug for its treatment. In the future, vorinostat may be involved in alleviating and inducing response either as a single agent or in combination with other agents. Due to their low toxicity profile and good overall efficacy, HDACis are ideal agents for concurrent usage. Although there is better evidence of vorinostat efficacy in hematologic malignancies (13) and diseases (myelofibrosis\textsuperscript{38} and myelodysplastic syndromes)\textsuperscript{17} than with solid tumors, there are enough data to support further vorinostat studies in solid tumors. Vorinostat has shown activity in ovarian cancer,\textsuperscript{8} in colon cancer in combination with sorafenib,\textsuperscript{9} and synergism and efficacy in lung cancer with carboplatin and taxol.\textsuperscript{11} Other chemotherapeutic agents which exhibit synergism include cisplatin, etoposide, bortezomib, and gemcitabine. The HDACis also exhibit synergism with differentiating agents as mentioned, including ATRA, imatinib (an inhibitor of the Bcr-Abl tyrosine kinase expressed by the Philadelphia chromosome in CML), the breast cancer drug trastuzumab (a monoclonal antibody against HER2/neu receptor), and 17 AAG (an inhibitor of oncogenic protein chaperone HSP90).\textsuperscript{2} More studies are ongoing and more HDACis are being developed and evaluated in a wide range of cancers and for use in different combinations, and this will hopefully result in increases in response and lower levels of toxicity.

**Disclosures**

The authors report no conflicts of interest.

**References**


