Role of Histone Deacetylase Inhibitors in the Treatment of Lymphomas and Multiple Myeloma

Jasmine Zain, MD

KEYWORDS

• Histone deacetylase inhibitors • Lymphoma • Multiple myeloma
• Epigenetic therapy

KEY POINTS

- Histone deacetylase inhibitors (HDACI) are epigenetic agents that affect the acetylation and deacetylation status of histones and other proteins, resulting in effects on gene expression and other important cellular functions.
- Epigenetic deregulation has been demonstrated in the pathogenesis of all types of lymphoma.
- HDACI as single agents have shown remarkable clinical activity in lymphomas, especially T cell lymphomas.
- The mechanism of the antilymphoma activity of HDACI is unknown.
- HDACI can be administered both orally and intravenously. They are well tolerated in the clinical setting, with a manageable side effect profile.
- Combining HDACI with other anticancer therapies, including cytotoxic therapies and targeted agents, is a promising new approach to the treatment of lymphomas.

Epigenetic processes are a means of affecting gene expression without altering the DNA nucleic acid sequence.[1–3] They are implicated in carcinogenesis, and epigenetic modification is an area of intense oncologic research for anticancer therapies in various human malignancies.[4] There are 3 fundamental modification processes that are of biologic significance in oncology: (1) acetylation and deacetylation of histones catalyzed by histone acetyl transferases (HATs) and histone deacetylases (HDACs); (2) genome methylation of CpG islands controlled by methylation and demethylation enzymes; and (3) small silencing RNA (siRNA)[5–7] that blocks gene expression. From a clinical perspective, biologic agents that modify the acetylation status of histones are important in the treatment of lymphoid malignancies. Presently, 2 HDACIs,

Division of Hematologic Malignancies and Medical Oncology, NYU Langone Medical Center, 7th Floor, 160 East 34th Street, New York, NY 10016, USA
E-mail address: Jasmine.zain@nyumc.org

Hematol Oncol Clin N Am 26 (2012) 671–704
doi:10.1016/j.hoc.2012.01.006 **hemonc.theclinics.com**
0889-8588/12/$ – see front matter

vorinostat and romidepsin, are approved for the treatment of relapsed and refractory cutaneous T cell lymphomas (CTCL),[8,9] and romidepsin is also approved for the treatment of relapsed and refractory peripheral T cell lymphomas (PTCL).[10]

Histone acetyl modifications occur in the context of nucleosomes, that are recurring packaging structures of 146 base pairs of DNA wrapped around a core of 8 histone proteins.[11] The amino end of these histone proteins extends outwards and can be modified by chemical process like acetylation, methylation, and phosphorylation modulated by the respective set of opposing enzymes that control these chemical reactions. By affecting their secondary structure, these modifications change the spatial relationship of the histone proteins, with the DNA strand making it more or less poised for the transcription machinery to reach the DNA strand and start the process of gene transcription and protein expression. Specifically, acetylation of the ε-amino moiety on the lysine tails of histones leads to an open or transcriptionally active state of chromatin allowing transcription to proceed. In contrast, deacetylation of lysine results in a closed, condensed chromatin that prevents access of the transcription machinery to the DNA strand, thus silencing transcription. These reactions are catalyzed by 2 major classes of enzymes, referred to as HATs and HDACs. There is another class of enzymes, called histone deacetylase inhibitors (HDACIs), which can block the function of HDACs by binding to and inactivating the catalytically active pocket of HDACs.[12] This prevents or reverses the deacetylated state of the histone and promotes transcription just like HATs. However, HDACIs are distinct from HATs and to date several compounds have been identified as having HDACI-like properties. They have therapeutic potential as anticancer agents as discussed below. There are other posttranslational modifications that can affect lysine and other amino acid residues on histones, as well as other cellular proteins, and secondarily affect their function. These modifications include methylation, ubiquitinylation, phosphorylation, glycosylation, and sumoylation. The proteins affected include, but are not limited to, transcription factors like p53, E2F, c-Myc, nuclear factor kB(NF-kB), hypoxia inducible factor (HIF-1a), estrogen, and androgen receptor complexes; DNA repair enzymes like Ku70; heat shock proteins (HSP) like HSP-90; signaling pathway intermediaries like signal transducer and activation of transcription 3 (STAT 3); and structural proteins like α-tubulin.[13] There are several reviews on epigenetic and posttranslational modification. This article focuses on the emerging role of HDACIs in the treatment of lymphomas and multiple myeloma (MM).

BIOLOGY OF HDACs

More than 18 different HDACs have been identified to date based on their homology to yeast proteins,[14] as shown in **Table1**. Class I, II, and IV HDACs require Zn^{2+} as a cofactor in their active site and are generally inhibited by pan-HDACI, but data are now emerging regarding the newer HDACIs that have selective activity against specific isoenzymes (eg, tubacin is an HDACI that only blocks the action of HDAC6). Class III HDACs, also known as sirutins, are homologous to the yeast Sir 2 protein[15] and require nicotinamide adenine dinucleotide (NAD+) as a coenzyme and are not affected by pan-HDACI. To date, there are no data to suggest that inhibiting one HDAC rather than another has any clinical benefit. The clinical significance of selective HDACs inhibition remains unclear.

BIOLOGY OF HDACI

HDACIs are classified into 4 structural groups that vary in their potency and their ability to block various classes of HDACs, as shown in **Table 2**. Besides the effects of HDAC