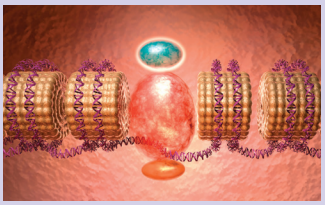
Histone Deacetylase Inhibitors:
Novel Agents in Cancer Treatment

Erica Glass, RN, BSN, MS, CRNP, and Pamela Hallquist Viale, RN, MS, CS, ANP, AOCNP®



Histone deacetylase inhibitors (HDAC-Is) are agents that have demonstrated anticancer activity in vivo and in vitro, leading to clinical trials evaluating their efficacy in multiple cancer types. Only two HDAC-Is are currently approved by the U.S. Food and Drug Administration, vorinostat and romidepsin, both with indications for cutaneous T-cell lymphoma. Romidepsin has an additional approval in peripheral T-cell lymphoma. Promising clinical trial results in other cancer types will likely lead to expanded use of these and other HDAC-Is. To provide care for patients receiving these agents, oncology nurses should be knowledgeable about the emerging role of HDAC-Is. This article reviews the mechanism of action of HDAC-Is, currently approved therapies, and nursing management of cutaneous T-cell lymphoma.

Erica Glass, RN, BSN, MS, CRNP, is an oncology nurse practitioner in medical oncology at St. Agnes Cancer Institute in Baltimore, MD, and Pamela Hallquist Viale, RN, MS, CS, ANP, AOCNP®, is an oncology nurse practitioner in Goleta, CA, and editor of the *Journal of the Advanced Practitioner in Oncology*. The authors take full responsibility for the content of the article. The authors were participants in the *Clinical Journal of Oncology Nursing (CJON)* Writing Mentorship Program. Viale received honorarium from the Oncology Nursing Society for her role as a mentor in the *CJON* Writing Mentorship Program. The content of this article has been reviewed by independent peer reviewers to ensure that it is balanced, objective, and free from commercial bias. No financial relationships relevant to the content of this article have been disclosed by the independent peer reviewers or editorial staff. Glass can be reached at ericaglass@hotmail.com, with copy to the editor at CJONEditor@ons.org. (First submission January 2012. Revision submitted March 2012. Accepted for publication March 30, 2012.)

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Histone deacetylase inhibitors (HDAC-Is) are emerging as novel targeted therapy agents and have been noted to be effective inhibitors of cancer growth and promoters of cell death (Bi & Jiang, 2006). Inhibitors of HDAC can be lethal to cancer cells; however, normal cells are relatively resistant to cell death induced by HDAC-Is (Bi & Jiang, 2006). Although agents in this class are currently only approved for two relatively rare malignancies, peripheral T-cell lymphoma (PTCL) and cutaneous T-cell lymphoma (CTCL), oncology nurses should be knowledgeable about HDAC-Is and ongoing clinical trials investigating the use of additional agents for other cancers.

Histone Deacetylase Inhibitors

Alteration of Gene Expression

Histone acetylatransferases (HATs) and HDACs are enzymes involved in the regulation of gene transcription in the human body. Genes, the basic units of inheritance and the instructions by which all cell processes occur, are held in cells in tightly wound structures called chromatins. Chromatin is composed of nucleosomes, which are made of DNA wrapped tightly around core histones (Thiagalingam et al., 2003). The process of gene replication requires the unwinding of DNA from the histones, and is regulated by enzymes that interact with the ends of the histone. When HAT interacts with a histone, an acetyl group is given to the histone end and the DNA is able to unwind for transcription (Pons et al., 2009). Conversely, when HDAC interacts with a histone, the acetyl group is removed, and the DNA is once again wound tightly to block transcription (see Figure 1). Inhibiting histone deacetylation, then, allows acetylation to occur, therefore allowing transcription to occur (Johnstone, 2002). Several other functions of HDACs in the body are hypothesized that also involve cell cycle regulation and cell survival. In addition to their interaction with histones, HDACs interact with nonhistone proteins, many of which are involved in regulation of cell proliferation. Proteins such as c-MYC, pRb, and p53 (a tumor suppressor gene) are involved in cell cycle regulation and, when interacting with HDACs, can upregulate or downregulate cell replication (Marks & Xu, 2009).

Eighteen known HDACs exist, each with a unique function and location within the cell. These HDACs are divided into four classes (class I–IV) and are organized by their homology to yeast proteins (Lane & Chabner, 2009). Classes I (HDACs 1, 2, 3, and 8), II (HDACs 4, 5, 7 and 9), and IV (HDAC 11) are the zinc-dependent classes, so named because of a zinc molecule