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NLM Citation: LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Vorinostat. [Updated 2016 Jun 5].
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Vorinostat

Updated: June 5, 2016.

OVERVIEW

Introduction

Vorinostat is an oral histone deacetylase inhibitor and antineoplastic agent that is approved for use in refractory or relapsed cutaneous T cell lymphoma. Vorinostat is associated with modest rate of minor serum enzyme elevations during therapy, but has not been linked to cases of clinically apparent liver injury.

Background

Vorinostat (vor in' oh stat) is an oral small molecule inhibitor of histone deacetylase which acts by preventing removal of acetyl groups from histones. The accumulation of acetyl groups on histones causes cell cycle arrest and apoptotic cell death. Malignant cells and particularly malignant T cells are particularly sensitive to the effects of inhibition of histone deacetylases. In open label studies in patients with refractory cutaneous T cell lymphoma (CTCL), monotherapy with vorinostat yielded an overall response rate of 30%, and some responders had long term remissions and were able to undergo hematopoietic cell transplantation. Vorinostat has also been evaluated in B cell lymphomas and in several forms of solid tumors, but with only modest results. Vorinostat was approved for use in the United States in 2006 as monotherapy for refractory or relapsing cutaneous T cell lymphoma, the first histone deacetylase inhibitor approved as an anticancer agent. Vorinostat is available in capsules of 100 mg under the commercial name Zolinza. The recommended dose is 400 mg daily by mouth, continuing therapy until there is disease progression or unacceptable toxicity. Side effects are common, but usually mild-to-moderate in severity, and include nausea, fatigue, fever, anemia, neutropenia, thrombocytopenia, constipation, rash, edema, cough and pruritus. Side effects lead to early discontinuation in up to 8% of patients. Severe adverse events can include marked neutropenia, thrombocytopenia, serious infections, sepsis and tumor lysis syndrome.

Hepatotoxicity

In clinical trials of vorinostat in patients with CTCL, the rates of serum enzyme elevations during therapy were rarely mentioned and only occasional episode of mild elevations were recorded. Minor elevations in serum ALT levels occurred in 15% to 45% of patients, but values above 5 times ULN were rare and there were no reports of hepatitis, jaundice or clinically apparent liver injury among the treated subjects. Vorinostat has had limited clinical use, but there have been no published reports of its association with significant liver injury.

Likelihood score: E (unlikely cause of clinically apparent liver injury).

Mechanism of Injury

The reason why vorinostat might cause serum enzyme elevations is not known, but may be a direct toxicity to hepatocytes caused by inhibition of histone deacetylase or other enzyme activities. Vorinostat is metabolized in the liver by glucuronidation and is not a substrate, inhibitor or inducer of cytochrome P450 enzymes.

Outcome and Management

Serum enzyme elevations can occur during vorinostat therapy, but they are usually transient and mild-to-moderate in severity, rarely requiring dose modification. There is no known cross sensitivity to hepatic injury among the different histone deacetylase inhibitors.

Drug Class: Antineoplastic Agents, Histone Deacetylase Inhibitors

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Vorinostat – Zolinza®

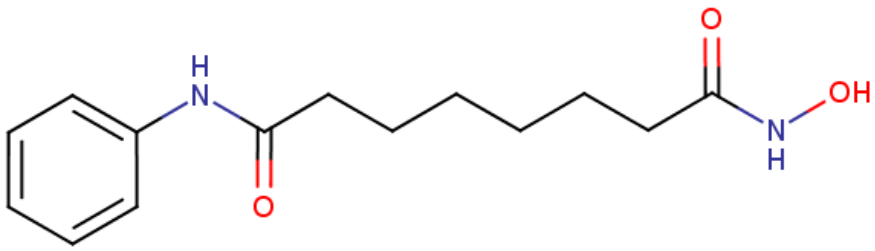
DRUG CLASS

Antineoplastic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO	MOLECULAR FORMULA	STRUCTURE
Vorinostat	149647-78-9	C14-H20-N2-O3	

ANNOTATED BIBLIOGRAPHY

References updated: 05 June 2016

Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999.

(Review of hepatotoxicity published in 1999 before the availability of histone deacetylase inhibitors).

DeLeve LD. Cancer chemotherapy. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, p. 549-68.

(Review of hepatotoxicity of cancer chemotherapeutic agents; does not discuss vorinostat).

Chabner BA, Barnes J, Neal J, Olson E, Mujagic H, Sequist L, Wilson W, et al. Targeted therapies: tyrosine kinase inhibitors, monoclonal antibodies, and cytokines. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 1731-54.

(Textbook of pharmacology and therapeutics).

Kelly WK, O'Connor OA, Krug LM, Chiao JH, Heaney M, Curley T, MacGregore-Cortelli B, et al. Phase I study of an oral histone deacetylase inhibitor, suberoylanilide hydroxamic acid, in patients with advanced cancer. J Clin Oncol 2005; 23: 3923-31. PubMed PMID: 15897550.

(Among 73 patients with different forms of advanced cancer treated with several regimens of vorinostat, the maximum tolerated dose was 400 mg daily and toxicities included fatigue, anorexia, nausea, diarrhea, bone marrow suppression, hyperglycemia, creatinine elevations and proteinuria; no mention of ALT elevations).

Olsen EA, Kim YH, Kuzel TM, Pacheco TR, Foss FM, Parker S, Frankel SR, et al. Phase IIb multicenter trial of vorinostat in patients with persistent, progressive, or treatment refractory cutaneous T-cell lymphoma. J Clin Oncol 2007; 25: 3109-15. PubMed PMID: 17577020.

(Among 74 patients with refractory or relapsed CTCL treated with vorinostat, the overall response rate was 30% and adverse events included diarrhea [49%], fatigue [46%], nausea [43%] and anorexia [26%]; no mention of ALT elevations or hepatotoxicity).

Duvic M, Talpur R, Ni X, Zhang C, Hazarika P, Kelly C, Chiao JH, et al. Phase 2 trial of oral vorinostat (suberoylanilide hydroxamic acid, SAHA) for refractory cutaneous T-cell lymphoma (CTCL). Blood 2007; 109: 31-9. PubMed PMID: 16960145.

(Among 33 patients with refractory or relapsed CTCL treated with vorinostat, the overall response rate was 24% and side effects were common, serious adverse events being dehydration, thrombocytopenia, vomiting, anemia, neutropenia and infections; no mention of ALT elevations or hepatotoxicity).

Vorinostat (Zolinza) for cutaneous T-Cell lymphoma. Med Lett Drugs Ther 2007; 49 (1256): 23-4. PubMed PMID: 17351559.

(Concise review of the mechanism of action, clinical efficacy, safety and costs of vorinostat shortly after its approval for use in the US; mentions serious adverse events of pulmonary embolism, squamous cell carcinoma of skin and fetal abnormalities).

Crump M, Coiffier B, Jacobsen ED, Sun L, Ricker JL, Xie H, Frankel SR, et al. Phase II trial of oral vorinostat (suberoylanilide hydroxamic acid) in relapsed diffuse large-B-cell lymphoma. Ann Oncol 2008; 19: 964-9. PubMed PMID: 18296419.

(Among 18 patients with relapsed B cell lymphoma treated with vorinostat, the overall response rate was 5% [1 patient] and serious adverse events occurred in 7 patients [39%], mostly hematologic and gastrointestinal events; no mention of ALT elevations or hepatotoxicity).

Duvic M, Olsen EA, Breneman D, Pacheco TR, Parker S, Vonderheid EC, Abuav R, et al. Evaluation of the long-term tolerability and clinical benefit of vorinostat in patients with advanced cutaneous T-cell lymphoma. Clin Lymphoma Myeloma 2009; 9: 412-6. PubMed PMID: 19951879.

(Six of the 74 patients with CTCL enrolled in a trial of vorinostat were treated for 2 years, all with only moderate toxicities).

Traynor AM, Dubey S, Eickhoff JC, Kolesar JM, Schell K, Huie MS, Groteluschen DL, et al. Vorinostat (NSC# 701852) in patients with relapsed non-small cell lung cancer: a Wisconsin Oncology Network phase II study. J Thorac Oncol 2009; 4: 522-6. PubMed PMID: 19347984.

(Among 18 patients with relapsed NSCLC treated with vorinostat, there were no partial or complete response and side effects were common; no mention of ALT elevations or hepatotoxicity).

Kavanaugh SM, White LA, Kolesar JM. Vorinostat: A novel therapy for the treatment of cutaneous T-cell lymphoma. Am J Health Syst Pharm 2010; 67: 793-7. PubMed PMID: 20479100.

(Review of the mechanism of action, pharmacology, clinical efficacy and safety of vorinostat therapy of cutaneous T cell lymphoma mentions an overall response rate of 30% and frequency of side effects including fatigue in 52%, nausea in 41%, but no mention of ALT elevations or hepatotoxicity).

Kirschbaum M, Frankel P, Popplewell L, Zain J, Delioukina M, Pullarkat V, Matsuoka D, et al. Phase II study of vorinostat for treatment of relapsed or refractory indolent non-Hodgkin's lymphoma and mantle cell lymphoma. J Clin Oncol 2011; 29: 1198-203. PubMed PMID: 21300924.

(Among 35 patients with non-Hodgkin lymphoma treated with vorinostat for an average of 6 months, overall response rates were 29% in follicular lymphoma, but 0% with mantle cell lymphoma; ALT or AST elevations occurred in 2 patients [3%], but both were transient and less than 3 times ULN).

Kirschbaum MH, Goldman BH, Zain JM, Cook JR, Rimsza LM, Forman SJ, Fisher RI. A phase 2 study of vorinostat for treatment of relapsed or refractory Hodgkin lymphoma: Southwest Oncology Group Study S0517. Leuk Lymphoma 2012; 53: 259-62. PubMed PMID: 21823829.

(Among 25 patients with refractory or relapsed Hodgkin lymphoma treated with vorinostat for an average of 3.8 months, the overall response rate was 8%; no mention of ALT elevations or hepatotoxicity).

Ogura M, Ando K, Suzuki T, Ishizawa K, Oh SY, Itoh K, Yamamoto K, et al. A multicentre phase II study of vorinostat in patients with relapsed or refractory indolent B-cell non-Hodgkin lymphoma and mantle cell lymphoma. Br J Haematol 2014; 165: 768-76. PubMed PMID: 24617454.

(Among 39 patients with follicular lymphoma treated with vorinostat, the overall response rate was 39%; adverse events were common, but no mention of ALT elevations or hepatotoxicity).

Duvic M, Dimopoulos M. The safety profile of vorinostat (suberoylanilide hydroxamic acid) in hematologic malignancies: A review of clinical studies. Cancer Treat Rev 2016; 43: 58-66. PubMed PMID: 26827693.

(Review of the adverse event rates in various trials of vorinostat and comparison to other histone deacetylase inhibitors reported a high rate of adverse events that were serious and drug related in 15% of patients and led to drug discontinuation in 8%; the most common side effects were diarrhea, nausea, fatigue and thrombocytopenia; only rare and occasional ALT elevation noted and no mention of hepatotoxicity or clinically apparent liver injury).