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Panobinostat

Updated: June 5, 2016.

OVERVIEW

Introduction

Panobinostat is an oral histone deacetylase inhibitor and antineoplastic agent that is approved for use in combination with other agents in refractory or relapsed multiple myeloma. Panobinostat 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

Panobinostat (pan" oh bin' oh stat) is an oral small molecule inhibitor of histone deacetylases, thereby preventing removal of acetyl groups from histones. The accumulation of acetyl groups on histones causes cell cycle arrest and apoptotic cell death. Malignant cells are particularly sensitive to the effects of inhibition of histone deacetylases. In open label studies in patients with multiple myeloma, panobinostat in combination with bortezomib (a proteasome inhibitor) yielded overall response rates of up to 50% and some responders had long term remissions. A large, controlled trial in patients with advanced, refractory multiple myeloma demonstrated prolongation of progression-free survival by the addition of panobinostat to bortezomib and dexamethasone, but the overall survival was not different at the time of the initial analysis. Nevertheless, panobinostat was given accelerated approval for use in the United States in 2015 to be used in combination with bortezomib and dexamethasone in patients with refractory or relapsed multiple myeloma. Panobinostat is available in capsules of 10, 15 or 20 mg under the brand name Farydak. The recommended dose regimen is 20 mg three times weekly for two weeks in three week cycles until there is disease progression or unacceptable toxicity. Side effects are common and may require dose modification. The most common adverse events are thrombocytopenia, leukopenia, anemia, diarrhea, nausea, vomiting, anorexia, fatigue, fever, peripheral edema, cough and pruritus. Panobinostat therapy has also been associated with hypokalemia, hypophosphatemia, hyponatremia and mild increases in serum creatinine. Uncommon, but serious adverse events include severe diarrhea and cardiovascular events such as cardiac ischemia, arrhythmias and EKG changes.

Hepatotoxicity

Most clinical trials of panobinostat have not reported rates of serum enzyme elevations during therapy and it is typically given in combination with other antineoplastic agents that can cause serum ALT and AST elevations. In the large controlled trial of panobinostat vs placebo in combination with bortezomib and dexamethasone, ALT elevations occurred in similar proportion of patients receiving panobinostat (31%) as placebo (38%) and values above 5 times the upper limit of normal were uncommon (1.8% and 1.3%). In addition, there have been no reports of clinically apparent liver injury with jaundice associated with panobinostat therapy. Thus, panobinostat

appears to have little hepatotoxic potential and liver injury from panobinostat must be quite rare, if it occurs at all.

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

Mechanism of Injury

The reason why panobinostat 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. Panobinostat is extensively metabolized in the liver by the cytochrome P450 system (predominantly CYP 3A4 and 2D6) and drug-drug interactions are likely to occur if it is used with other agents that are inducers, inhibitors or major substrates of these microsomal enzymes.

Outcome and Management

Serum enzyme elevations are uncommon during panobinostat therapy and are rarely dose limiting. Nevertheless, regular monitoring of liver tests with each course of therapy is recommended with more frequent monitoring if serum aminotransferase values rise. Panobinostat should be held if ALT or AST values rise above 5 times the ULN, and elevations of more than 20 times the ULN, or appearance of jaundice or symptoms of liver injury should trigger permanent discontinuation. 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

Panobinostat – Farydak®

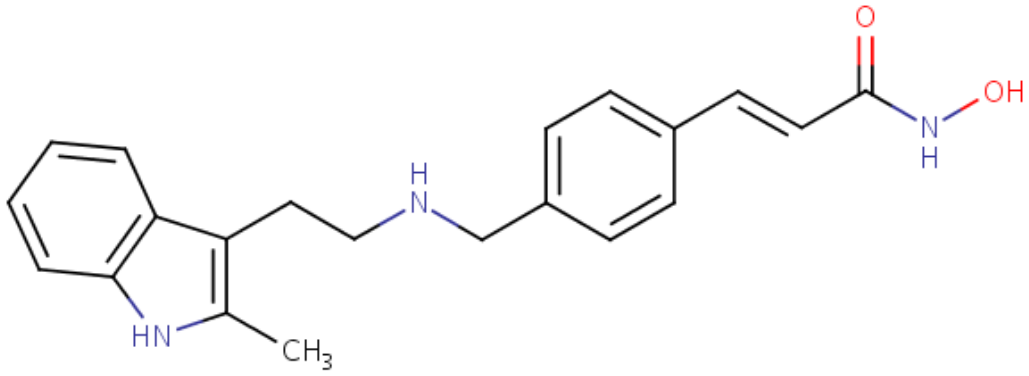
DRUG CLASS

Antineoplastic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO	MOLECULAR FORMULA	STRUCTURE
Panobinostat	404950-80-7	C21-H23-N3-O2	

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 panobinostat).

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).

Ellis L, Pan Y, Smyth GK, George DJ, McCormack C, Williams-Truax R, Mita M, et al. Histone deacetylase inhibitor panobinostat induces clinical responses with associated alterations in gene expression profiles in cutaneous T-cell lymphoma. Clin Cancer Res 2008; 14: 4500-10. PubMed PMID: 18628465.

(Among 10 patients with refractory CTCL given different doses of panobinostat, 6 had a clinical response and the optimal dose was 20 mg [given Monday, Wednesday and Friday], tumor gene expression changing with treatment, often with suppression of genes governing apoptosis, angiogenesis and immune modulation).

Duvic M, Dummer R, Becker JC, Poulalhon N, Ortiz Romero P, Grazia Bernengo M, Lebbé C, et al. Panobinostat activity in both bexarotene-exposed and -naïve patients with refractory cutaneous T-cell lymphoma: results of a phase II trial. Eur J Cancer 2013; 49: 386-94. PubMed PMID: 22981498.

(Among 139 patients with refractory CTCL treated with panobinostat [20 mg thrice weekly] for an average of 3 months, the overall response rate was 17% and common side effects were thrombocytopenia [47%], diarrhea [42%], fatigue [33%], nausea [32%], anorexia [21%], neutropenia [15%] and creatinine elevation [13%]; no mention of ALT elevations or hepatotoxicity).

Ghobrial IM, Campigotto F, Murphy TJ, Boswell EN, Banwait R, Azab F, Chuma S, et al. Results of a phase 2 trial of the single-agent histone deacetylase inhibitor panobinostat in patients with relapsed/refractory Waldenström macroglobulinemia. Blood 2013; 121: 1296-303. PubMed PMID: 23287861.

(Among 36 patients with Waldenström macroglobulin treated with panobinostat [25 or 30 mg three times weekly] for an average of 5 months, responses occurred in 17 [47%], but adverse events were frequent including diarrhea in 83%, thrombocytopenia 78%, neutropenia 69%, anemia 60%; no mention of ALT elevations or hepatotoxicity).

Cassier PA, Lefranc A, Amela EY, Chevreau C, Bui BN, Lecesne A, Ray-Coquard I, et al. A phase II trial of panobinostat in patients with advanced pretreated soft tissue sarcoma. A study from the French Sarcoma Group. Br J Cancer 2013; 109: 909-14. PubMed PMID: 23922114.

(Among 47 patients with refractory, advanced soft tissue sarcoma treated with panobinostat [40 or 20 mg thrice weekly], the overall response rate was 0% and adverse events were common leading to a lowering of study dose; no mention of ALT elevations or hepatotoxicity).

San-Miguel JF, Richardson PG, Günther A, Sezer O, Siegel D, Bladé J, LeBlanc R, et al. Phase Ib study of panobinostat and bortezomib in relapsed or relapsed and refractory multiple myeloma. J Clin Oncol 2013; 31: 3696-703. PubMed PMID: 24019544.

(Among 47 patients with refractory multiple myeloma treated with the combination of panobinostat and bortezomib in various dose regimens, the overall response rate was 52% and toxicity was common, but manageable; no mention of ALT elevations or hepatotoxicity).

San-Miguel JF, Hungria VT, Yoon SS, Beksac M, Dimopoulos MA, Elghandour A, Jedrzejczak et al. Panobinostat plus bortezomib and dexamethasone versus placebo plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma: a multicentre, randomised, double-blind phase 3 trial. Lancet Oncol 2014; 15: 1195-206. PubMed PMID: 25242045.

(Among 768 patients with refractory multiple myeloma treated with bortezomib and dexamethasone combined with either panobinostat [20 mg thrice weekly for 2 weeks in 3 week cycles] or placebo with follow up of 6 to 47 months, progression-free, but not overall survival was longer with panobinostat therapy; adverse events that were more frequent with panobinostat included diarrhea, nausea, fatigue, thrombocytopenia and neutropenia; rates of serum ALT elevations were similar in the two groups [any: 31% vs 38%, and above 5 times ULN: 1.8% vs 1.3%]).

Slingerland M, Hess D, Clive S, Sharma S, Sandstrom P, Loman N, Porro MG, et al. A phase I, open-label, multicenter study to evaluate the pharmacokinetics and safety of oral panobinostat in patients with advanced solid tumors and various degrees of hepatic function. Cancer Chemother Pharmacol 2014; 74: 1089-98. PubMed PMID: 25253045.

(Pharmacokinetic study of panobinostat in 25 patients with advanced malignancy, found higher peak serum levels in patients with hepatic dysfunction than in those without, but similar rate of adverse events).

Berdeja JG, Hart LL, Mace JR, Arrowsmith ER, Essell JH, Owera RS, Hainsworth JD, et al. Phase I/II study of the combination of panobinostat and carfilzomib in patients with relapsed/refractory multiple myeloma. Haematologica 2015; 100: 670-6. PubMed PMID: 25710456.

(Among 44 patients with advanced, refractory multiple myeloma treated with the combination of panobinostat [30 mg] and carfilzomib [20 or 45 mg/m^2] in varying regimens, the overall response rate was 67% and adverse events were common, but manageable in most patients; ALT increases above 5 times ULN occurred in only 1 patient [2%]).

Panobinostat (Farydak) for multiple myeloma. Med Lett Drugs Ther 2015; 57: e118-9. PubMed PMID: 26262884.

(Concise summary of the mechanism of action, clinical efficacy, safety and costs of panobinostat shortly after it was approved for use in multiple myeloma in the US, mentions that severe side effects include diarrhea, cytopenias, prolongation of the QTc interval and that "hemorrhage, infections and hepatotoxicity have also been reported").

Laubach JP, Moreau P, San-Miguel JF, Richardson PG. Panobinostat for the treatment of multiple myeloma. Clin Cancer Res 2015; 21: 4767-73. PubMed PMID: 26362997.

(Review of the mechanism of action, pharmacology, clinical efficacy and toxicity of panobinostat as therapy of advanced multiple myeloma, mentions gastrointestinal and hematologic adverse events, but not ALT elevations or hepatotoxicity).