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Sonidegib

Updated: June 1, 2017.

OVERVIEW

Introduction

Sonidegib is a small molecule kinase inhibitor that blocks signaling in the hedgehog pathway and is used in the therapy of unresectable or metastatic basal cell carcinoma. Sonidegib therapy is associated with a low rate or transient serum aminotransferase elevations during therapy, but has not been linked to instances of clinically apparent acute liver injury.

Background

Sonidegib (soe" ni deg' ib) is an orally available, kinase inhibitor with specific activity against a key step (activation of smoothened: SMO) in the hedgehog signaling pathway. Hedgehog is a key regulator of embryonic development, cell growth and differentiation. Mutations in this pathway have been identified in several malignant diseases including basal cell carcinoma. Clinical trials of sonidegib in patients with metastatic or locally advanced basal cell carcinoma have reported at least partial responses in up to 58% of patients. Sonidegib was approved for use in the United States in 2015, the second hedgehog pathway inhibitor approved for oral treatment of advanced basal cell carcinoma that is refractory or not amenable to treatment with surgery or radiation. Sonidegib is available in capsules of 200 mg under the brand name Odomzo. The recommended dose is 200 mg once daily until disease progression or unacceptable toxicity occurs. Side effects are frequent and often dose limiting although rarely life-threatening. Common side effects are similar to those reported with other inhibitors of the hedgehog signaling pathway and include muscle spasms, alopecia, anorexia, dysguesia, weight loss, nausea, diarrhea, fatigue, abdominal pain, headache, muscle and joint pains and serum creatine kinase (CK) elevations. Rare, but potentially severe adverse events include musculoskeletal adverse reactions and embryo-fetal toxicity.

Hepatotoxicity

Most clinical trials of sonidegib included few patients and rates of liver tests abnormalities were often not reported. In isolated trials, serum ALT elevations were reported in 15% to 27% of patients and to rise above 5 times the upper limit of normal (ULN) in 1% to 6%. Rates of serum enzyme elevations were greater with higher doses, and all were apparently transient and resolved either spontaneously or with dose reductions or discontinuation. In these trials, there were no cases of clinically apparent liver injury, hepatitis with jaundice or death from liver failure. The product label for sonidegib mentions serum enzyme elevations as a possible adverse event, but does not mention liver injury with jaundice or hepatic failure. Since its approval and more widespread use, there have been no published cases of hepatotoxicity attributed to sonidegib, but it is an uncommonly used antineoplastic agent. Serum enzyme elevations were also rare with the initial hedgehog inhibitor, vismodegib,

which has been implicated in causing at least one case of acute, self-limited cholestatic hepatitis (Case 1 in Vismodegib).

Likelihood score: E* (unproven but suspected cause of clinically apparent liver injury).

Mechanism of Injury

The cause of serum enzyme elevations during sonidegib therapy is unknown. Sonidegib is metabolized in the liver predominantly by CYP 3A and liver injury might be caused by a toxic or immunogenic metabolite. Alternatively, inhibition of the hedgehog pathway in hepatocytes may cause some degree of hepatic injury. Because sonidegib is a substrate for CYP 3A4, it is susceptible to drug-drug interactions with inducers or inhibitors of this microsomal enzyme.

Outcome and Management

In using kinase inhibitors for treatment of cancer, serum aminotransferase elevations above 5 times the upper limit of normal (if confirmed) or any elevations accompanied by jaundice or symptoms should lead to dose reduction or temporary cessation. The various protein kinase inhibitors vary greatly in chemical structure and there is little evidence for cross sensitivity to the liver injury.

Drug Class: Antineoplastic Agents, Protein Kinase Inhibitors

Related Drugs: Vismodegib

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Sonidegib – Odomzo®

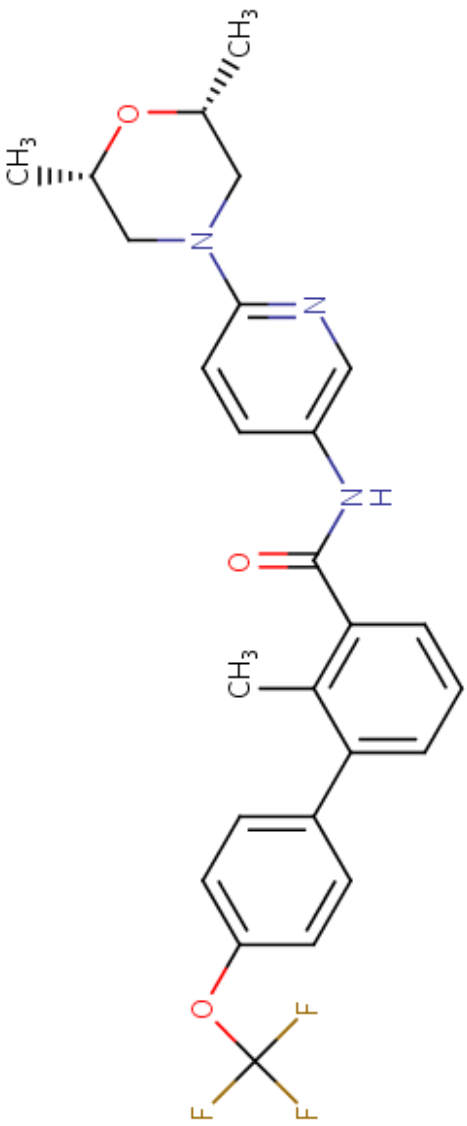
DRUG CLASS

Antineoplastic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Sonidegib	956697-53-3	C26-H26-F3-N3-O3	

ANNOTATED BIBLIOGRAPHY

References updated: 01 June 2017

Abbreviations used: CK, creatine kinase

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 protein kinase inhibitors such as sonidegib).

DeLeve LD. Kinase inhibitors. Cancer chemotherapy. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 556-7.

(Review of hepatotoxicity of cancer chemotherapeutic agents discusses several tyrosine kinase inhibitors including imatinib, gefitinib, erlotinib and crizotinib, but not sonidegib).

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).

Pan S, Wu X, Jiang J, Gao W, Wan Y, Cheng D, Han D, et al. Discovery of NVP-LDE225, a potent and selective smoothened antagonist. ACS Med Chem Lett 2010; 1: 130-4. PubMed PMID: 24900187.

(In vitro demonstration of selective antagonism of the kinase receptor smoothened by a novel series of chemicals identified by high throughput screening for molecules that inhibited the hedgehog signaling pathway).

Tang JY, Mackay-Wiggan JM, Aszterbaum M, Yauch RL, Lindgren J, Chang K, Coppola C, et al. Inhibiting the hedgehog pathway in patients with the basal-cell nevus syndrome. N Engl J Med 2012; 366: 2180-8. PubMed PMID: 22670904.

(Among 41 patients with basal cell nevus syndrome, vismodegib therapy was associated with a lower rate of new tumors and decrease in size of existing tumors compared to placebo, but was associated with a high rate of side effects and 54% stopped therapy because of side effects; no mention of ALT elevations or hepatotoxicity).

Rodon J, Tawbi HA, Thomas AL, Stoller RG, Turtschi CP, Baselga J, Sarantopoulos J, et al. A phase I, multicenter, open-label, first-in-human, dose-escalation study of the oral smoothened inhibitor sonidegib (LDE225) in patients with advanced solid tumors. Clin Cancer Res 2014; 20: 1900-9. PubMed PMID: 24523439.

(Among 103 patients with different forms of advanced cancer treated with increasing doses of sonidegib, dose limiting toxicities were myalgia and increases in serum creatine kinase [CK] levels, while common side effects were muscle spasms, myalgia, gastrointestinal complaints, fatigue and alopecia, ALT elevations occurred in 15% of patients and were above 5 times ULN in 6%).

Migden MR, Guminski A, Gutzmer R, Dirix L, Lewis KD, Combemale P, Herd RM, et al. Treatment with two different doses of sonidegib in patients with locally advanced or metastatic basal cell carcinoma (BOLT): a multicentre, randomised, double-blind phase 2 trial. Lancet Oncol 2015; 16: 716-28. PubMed PMID: 25981810.

(Among 230 patients with advanced basal cell carcinoma treated with sonidegib [200 vs 800 mg daily] for a median of 14 months, objective response rates were similar for both doses [36% vs 34%], but adverse event rates were less with the lower dose, including muscle spasms [49% vs 69%] and ALT elevations [1% vs 4%]).

Minami H, Ando Y, Ma BB, Hsiang Lee J, Momota H, Fujiwara Y, Li L, et al. Phase I, multicenter, open-label, dose-escalation study of sonidegib in Asian patients with advanced solid tumors. Cancer Sci. 2016; 107: 1477-83. PubMed PMID: 27467121.

(Among 45 Asian adults with advanced cancer treated with increasing doses of sonidegib [400 to 800 mg daily], the most common adverse events were myalgia, fatigue and CK elevations while ALT elevations occurred in 27% and were above 5 times ULN in 14%).

Lacouture ME, Dréno B, Ascierto PA, Dummer R, Basset-Seguin N, Fife K, Ernst S, et al. Characterization and management of hedgehog pathway inhibitor-related adverse events in patients with advanced basal cell carcinoma. Oncologist 2016; 21: 1218-29. PubMed PMID: 27511905.

(Review of the adverse events caused by vismodegib and sonidegib including muscle spasms, gastrointestinal complaints and alopecia, but does not discuss ALT elevations or liver related events).

Dummer R, Guminski A, Gutzmer R, Dirix L, Lewis KD, Combemale P, Herd RM, et al. The 12-month analysis from Basal Cell Carcinoma Outcomes with LDE225 Treatment (BOLT): A phase II, randomized, double-blind study of sonidegib in patients with advanced basal cell carcinoma. J Am Acad Dermatol 2016; 75: 113-25.e5. PubMed PMID: 27067394.

(Among the 230 patients with advanced basal cell cancer enrolled in a clinical trial comparing 200 vs 800 mg doses of sonidegib [Migden 2015], 12 month objective response rates were 58% vs 44% and discontinuation rates for adverse events were 28% vs 37%, mostly for muscle spasms and CK elevations; no mention of ALT elevations or hepatotoxicity).

Jacobsen AA, Aldahan AS, Hughes OB, Shah VV, Strasswimmer J. Hedgehog pathway inhibitor therapy for locally advanced and metastatic basal cell carcinoma: a systematic review and pooled analysis of interventional studies. JAMA Dermatol 2016; 152: 816-24. PubMed PMID: 27096888.

(Systematic review of 11 publications on vismodegib and 2 on sonidegib as therapy for advanced basal cell carcinoma provides summary of efficacy outcomes and rates of side effects, but does not discuss ALT elevations or hepatotoxicity).

Danial C, Sarin KY, Oro AE, Chang AL. An investigator-initiated open-label trial of sonidegib in advanced basal cell carcinoma patients resistant to vismodegib. Clin Cancer Res 2016; 22: 1325-9. PubMed PMID: 26546616.

(Among 9 patients with advanced basal cell carcinoma who were resistant to vismodegib therapy and were treated with sonidegib, none had an objective response and side effects included muscle cramps, nausea and CK elevations; ALT levels were not mentioned).

Sonidegib (Odomzo) for basal cell carcinoma. Med Lett Drugs Ther 2016; 58 (1489): 31-2. PubMed PMID: 26938701.

(Concise review of the mechanism of action, efficacy, safety and costs of sonidegib shortly after its approval for use in the US; mentions the common side effects of muscle spasms, CK elevations, gastrointestinal complaints, fatigue and alopecia, but does not mention ALT elevations or hepatotoxicity).

Casey D, Demko S, Shord S, Zhao H, Chen H, He K, Putman A, et al. FDA approval summary: sonidegib for locally advanced basal cell carcinoma. Clin Cancer Res 2017; 23 (10): 2377-81. PubMed PMID: 28073840.

(Summary of result of the clinical trials that formed the basis of the FDA approval of sonidegib for advanced basal cell carcinoma discusses overall safety results and specific issues of musculoskeletal and embryo-fetal toxicities, but not ALT elevations or hepatotoxicity).