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Axitinib

Updated: August 1, 2017.

OVERVIEW

Introduction

Axitinib is an oral tyrosine kinase inhibitor selective for vascular endothelial growth factor (VEGF) receptors -1, -2 and -3 that is used in the therapy of advanced renal cell carcinoma. Axitinib therapy is commonly associated with transient elevations in serum aminotransferase that are generally mild and asymptomatic. Axitinib has yet to be linked to instances of clinically apparent acute liver injury.

Background

Axitinib (Ax i' ti nib) is an orally available tyrosine kinase inhibitor with activity against the receptors for vascular endothelial growth factor (VEGF). Engagement of these receptors by VEGF is associated with cell growth and angiogenesis, pathways that stimulate tumor growth. Axitinib also has activity against c-KIT (a tyrosine kinase receptor, mutations of which are found in gastrointestinal stromal tumors) and platelet derived growth factor (PDGF) receptor. Preclinical studies demonstrated that axitinib has activity against several solid tumors in animal models. Clinical trials of axitinib in malignant diseases in humans showed activity against renal cell carcinoma and lesser effects in breast and gastric cancer. Axitinib received approval for use in the United States in 2012 for therapy of advanced renal cell carcinoma. Axitinib is available in tablets of 1 and 5 mg under the brand name Inlyta. The typical dose is 5 mg twice daily, which can be increased if well tolerated. Common side effects include fatigue, diarrhea, hypertension, anorexia, weight loss, nausea, hoarseness, hand-foot syndrome, constipation, arthralgias, abdominal discomfort, headache and rash. Uncommon side effects include venous thrombosis and gastrointestinal perforation.

Hepatotoxicity

In large clinical trials of axitinib, elevations in serum aminotransferase levels were common, occurring in up to 25% of patients. Values greater than 5 times the upper limit of normal (ULN), however, were uncommon, occurring in 1% to 2% of recipients. Furthermore, no instances of clinically apparent liver injury from axitinib were reported in prelicensure studies or during the more wide scale use since its approval. Nevertheless, periodic monitoring of liver tests during axitinib therapy is recommended.

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

Mechanism of Injury

The mechanism of injury accounting for serum enzyme elevations during axitinib therapy is not known. Axitinib is metabolized in the liver largely through the CYP 3A4 pathway and liver injury may be related to

production of a toxic intermediate. Axitinib is susceptible to drug-drug interactions with agents that inhibit or induce hepatic CYP 3A4 activity.

Outcome and Management

Serum aminotransferase elevations above 5 times the upper limit of normal (if confirmed) should lead to dose reduction or temporary cessation. Axitinib has not been implicated in cases of acute liver failure, chronic hepatitis or vanishing bile duct syndrome. There does not appear to be cross reactivity in risk for hepatic injury between axitinib and other tyrosine kinase inhibitors and, in some situations, switching to another tyrosine kinase receptor inhibitor may be appropriate.

Drug Class: Antineoplastic Agents, Protein Kinase Inhibitors

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Axitinib – Inlyta®

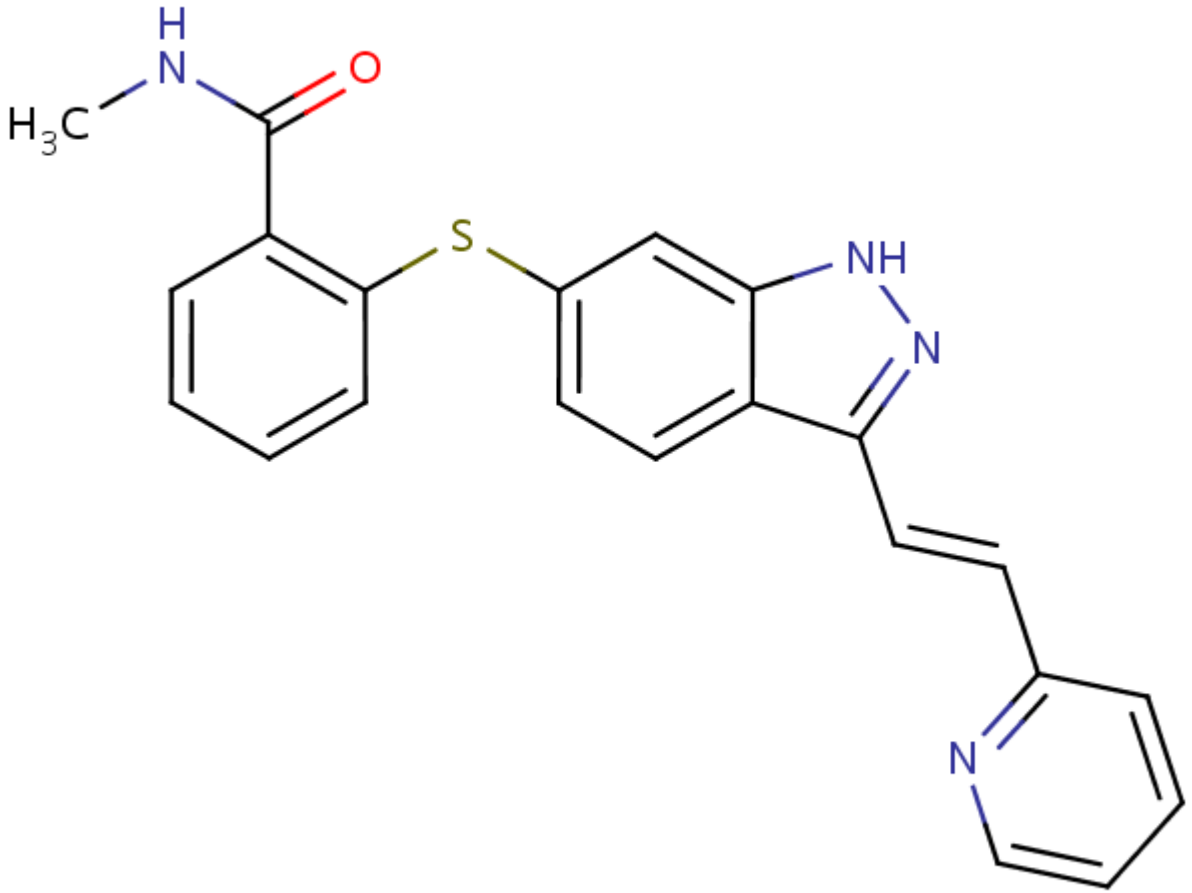
DRUG CLASS

Antineoplastic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Axitinib	319460-85-0	C22-H18-N4-O-S	

ANNOTATED BIBLIOGRAPHY

References updated: 01 August 2017

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 kinase inhibitors such as axitinib).

DeLeve LD. Cancer chemotherapy. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 541-67.

(Review of hepatotoxicity of cancer chemotherapeutic agents; imatinib, gefitinib, erlotinib and crizotinib are discussed, but not axitinib).

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).

Rixe O, Bukowski RM, Michaelson MD, Wilding G, Hudes GR, Bolte O, Motzer RJ, et al. Axitinib treatment in patients with cytokine-refractory metastatic renal-cell cancer: a phase II study. Lancet Oncol 2007; 8: 975-84. PubMed PMID: 17959415.

(Among 52 patients with metastatic renal cell cancer treated with axitinib, objective responses occurred in 44%; common side effects included fatigue, hypertension and diarrhea; no mention of ALT elevations or hepatotoxicity).

Fruehauf J, Lutzky J, McDermott D, Brown CK, Meric JB, Rosbrook B, Shalinsky DR, et al. Multicenter, phase II study of axitinib, a selective second-generation inhibitor of vascular endothelial growth factor receptors 1, 2, and 3, in patients with metastatic melanoma. Clin Cancer Res 2011; 17: 7462-9. PubMed PMID: 21976544.

(Among 32 patients with refractory melanoma, 37% showed some evidence of beneficial response to axitinib; rates of ALT elevations and hepatotoxicity were not mentioned).

Rugo HS, Stopeck AT, Joy AA, Chan S, Verma S, Lluch A, Liau KF, et al. Randomized, placebo-controlled, double-blind, phase II study of axitinib plus docetaxel versus docetaxel plus placebo in patients with metastatic breast cancer. J Clin Oncol 2011; 29: 2459-65. PubMed PMID: 21555686.

(Among 168 patients with refractory metastatic breast cancer, objective responses occurred in 24% on docetaxel alone vs 44% on docetaxel and axitinib; side effects were greater with combination therapy, but ALT elevations and hepatotoxicity were not mentioned).

Rini BI, Escudier B, Tomczak P, Kaprin A, Szczylik C, Hutson TE, Michaelson MD, et al. Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial. Lancet 2011; 378 (9807): 1931-9. PubMed PMID: 22056247.

(Among 723 patients with advanced renal cell carcinoma, progression free survival was longer with axitinib [6.7 months] than sorafenib [4.7 months], but that side effects were common, although rates of hepatotoxicity or ALT elevations were not provided).

Axitinib (Inlyta) for advanced renal cell carcinoma. Med Lett Drugs Ther 2012; 54 (1392): 47-8. PubMed PMID: 22683928.

(Concise review of the pharmacology, efficacy and safety of axitinib for renal cell carcinoma shortly after its approval in the US mentions that side effects can include elevations in serum aminotransferase levels).

Motzer RJ, Escudier B, Tomczak P, Hutson TE, Michaelson MD, Negrier S, Oudard S, et al. Axitinib versus sorafenib as second-line treatment for advanced renal cell carcinoma: overall survival analysis and updated results from a randomised phase 3 trial. Lancet Oncol 2013; 14: 552-62. PubMed PMID: 23598172.

(Among 723 patients with metastatic renal cell cancer treated with either axitinib or sorafenib, median overall survivals were similar with both agents [20.1 vs 19.2 months] and side effects were common; no mention of ALT elevations or hepatotoxicity).

Hutson TE, Lesovoy V, Al-Shukri S, Stus VP, Lipatov ON, Bair AH, Rosbrook B, et al. Axitinib versus sorafenib as first-line therapy in patients with metastatic renal-cell carcinoma: a randomised open-label phase 3 trial. Lancet Oncol 2013; 14: 1287-94. PubMed PMID: 24206640.

(Among 288 patients with metastatic renal cell carcinoma treated with either axitinib or sorafenib, progression free survival was similar in the two groups; side effects of diarrhea, hypertension, anorexia, weight loss and hoarseness were more common with axitinib; rates of ALT elevations and hepatotoxicity were not reported).

Rini BI, Melichar B, Ueda T, Grünwald V, Fishman MN, Arranz JA, Bair AH, et al. Axitinib with or without dose titration for first-line metastatic renal-cell carcinoma: a randomized double-blind phase 2 trial. Lancet Oncol 2013; 14: 1233-42. PubMed PMID: 24140184.

(Among 213 patients with metastatic renal cell carcinoma treated with standard or titrated doses of axitinib, side effects were more common with high doses, particularly hypertension, hand-foot syndrome and vomiting; ALT elevations occurred in 9% of patients, but were ≥5 times ULN in only 2%).

Shah RR, Morganroth J, Shah DR. Hepatotoxicity of tyrosine kinase inhibitors: clinical and regulatory perspectives. Drug Saf 2013; 36: 491-503. PubMed PMID: 23620168.

(Review of the hepatotoxicity of 18 tyrosine kinase inhibitors approved for use in cancer in the US as of 2013; axitinib has been reported to cause ALT elevations in up to 22% of patients [5 times ULN in < 1%], but has not been reported to cause hepatitis or hepatic failure).

Bracarda S, Castellano D, Procopio G, Sepúlveda JM, Sisani M, Verzoni E, Schmidinger M. Axitinib safety in metastatic renal cell carcinoma: suggestions for daily clinical practice based on case studies. Expert Opin Drug Saf 2014; 13: 497-510. PubMed PMID: 24641566.

(Review of published literature on side effects of axitinib and their management; no discussion of hepatotoxicity or ALT elevations).

Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, et al.; United States Drug Induced Liver Injury Network. Features and outcomes of 899 patients with drug-induced liver injury: The DILIN Prospective Study. Gastroenterology 2015; 148: 1340-52.e7. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, 49 [5%] were due to antineoplastic agents, including 9 [1%] to protein kinase inhibitors, but none were attributed specifically to axitinib).

Miyake H, Harada KI, Ozono S, Fujisawa M. Assessment of efficacy, safety, and quality of life of 124 patients treated with axitinib as second-line therapy for metastatic renal-cell carcinoma: experience in real-world clinical practice in Japan. Clin Genitourin Cancer 2017; 15: 122-8. *(Among 124* PubMed PMID: 27473522.

Japanese patients with renal cell carcinoma treated with axitinib, none had a complete response but 17% had a partial response, and side effects included hypertension [59%], dysphonia [55%], diarrhea [52%], hand-foot syndrome [50%], fatigue [43%] and hypothyroidism [43%]; no mention of ALT elevations or hepatotoxicity).

MacLean E, Cisar L, Mehle K, Eremina D, Quigley JM. Real-world axitinib use in the United States: a retrospective study using linked datasets. J Manag Care Spec Pharm 2016; 22: 723-32. PubMed PMID: 27231799.

(A "real-world" assessment of use of axitinib in the US made no mention of side effects or toxicity).

Kang YK, Yau T, Park JW, Lim HY, Lee TY, Obi S, Chan SL, et al. Randomized phase II study of axitinib versus placebo plus best supportive care in second-line treatment of advanced hepatocellular carcinoma. Ann Oncol 2015; 26: 2457-63. PubMed PMID: 26386123.

(Among 202 patients with advanced liver cancer treated with axitinib or placebo, overall survival was the same in the two groups, while side effects were more common with axitinib including ALT elevaions [74% vs 51%] with values above 5 times ULN in 10% vs 4%] and one axitinib treated patient died to acute liver failure).