U.S. National Library of Medicine
National Center for Biotechnology Information

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-. Tivozanib. [Updated 2023 Dec 26].
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Tivozanib

Updated: December 26, 2023.

OVERVIEW

Introduction

Tivozanib is a small molecule multi-kinase inhibitor that is used in the treatment of relapsed or refractory renal cell carcinoma. Tivozanib is associated with transient and usually mild elevations in serum aminotransferase during therapy and but has not been linked instances of clinically apparent acute liver injury.

Background

Tivozanib (tye voe' za nib) is an orally available, small molecule multi-kinase inhibitor which is used as a third line treatment of relapsed or refractory renal cell carcinoma. Tivozanib inhibits multiple tyrosine kinases, including vascular endothelial growth factor receptor (VEGFR)-1, VEGFR-2, VEGFR-3, c-kit, and platelet derived growth factor receptor beta (PDGFR-β). These kinases are often overexpressed in cancer cells, and VEGFRs are frequently found in renal cell cancers. Tivozanib had growth inhibitory activity in vitro and in vivo against renal cell cancer cell lines. In a randomized controlled trial in patients with relapsed or refractory renal cell cancer, tivozanib was found to be associated with a longer progression free survival than sorafenib. On the basis of these results, tivozanib was approved in the United States in 2021 as therapy of patients with relapsed or refractory advanced renal cell carcinoma following two or more prior therapies. Tivozanib is available in capsules of 1.34 and 0.89 mg under the brand name Fotivda. The recommended dose is 1.34 mg once daily for 21 days of 28-day cycles to continue until disease progression or unacceptable toxicity. Common side effects include hypertension, and symptoms of fatigue, diarrhea, decreased appetite, nausea, dysphonia, cough, and stomatitis. Therapy is also associated with hypothyroidism and decreases in serum sodium and phosphate. Less common but potentially severe adverse events include severe hypertension and hypertensive crisis, heart failure, arterial and venous thrombotic events, hemorrhage, proteinuria, thyroid dysfunction, impaired wound healing, reversible posterior leukoencephalopathy, and embryo-fetal toxicity.

Hepatotoxicity

In the published preregistration clinical trials of tivozanib, rates of serum ALT or AST elevations ranged from 10% to 29%, with 1% to 4% of treated patients having elevations above 5 times the upper limit of normal (ULN). Instances of clinically apparent liver injury including deaths with hepatic failure were reported in some clinical trials, but in all cases were attributed to hepatic metastases or to other underlying liver diseases. Since its approval and more widespread clinical use, there have been no reports of clinically apparent liver injury or hepatic failure attributed to tivozanib, but it has had limited clinical use.

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

Mechanism of Injury

Tivozanib therapy has been clearly linked to serum enzyme elevations the cause of which is unknown, but similar rates and patterns of liver test abnormalities have been reported with many kinase inhibitors and particularly with multi-kinase inhibitors such as tivozanib. Tivozanib is metabolized in the liver largely by CYP 3A and liver injury may be due to metabolism to an immunogenic or toxic intermediate. Tivozanib is also susceptible to drug-drug interactions with inducers or inhibitors of CYP 3A4.

Outcome and Management

Tivozanib has been clearly linked to serum aminotransferase elevations but has not been clearly linked to clinically apparent liver injury. The product label for tivozanib does not recommend routine monitoring of liver tests. But if found, serum aminotransferase elevations above 5 times ULN should lead to dose reduction or temporary cessation until the elevations are shown to have another cause or decrease into the normal or near normal range. ALT or AST elevations above 20 times ULN or any elevations accompanied by jaundice or symptoms should lead to discontinuation. There does not appear to be cross reactivity in risk for hepatic injury among the various kinase inhibitors but few instances have been studied.

Drug Class: Antineoplastic Agents, Protein Kinase Inhibitors

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Tivozanib – Fotivda®

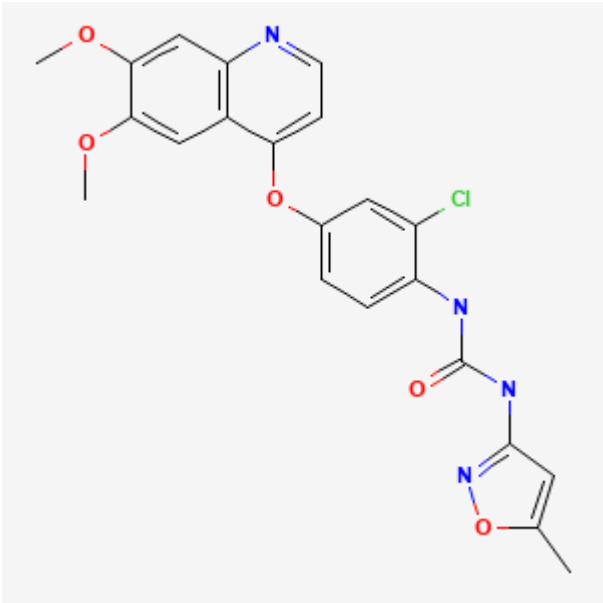
DRUG CLASS

Antineoplastic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Tivozanib	475108-18-0	C22-H19-Cl-N4-O5	

ANNOTATED BIBLIOGRAPHY

References updated: 26 December 2023

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 tyrosine kinase inhibitors such as tivozanib).

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

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

Wellstein A, Giaccone G, Atkins MB, Sausville EA. Pathway-targeted therapies: monoclonal antibodies, protein kinase inhibitors, and various small molecules. In, Brunton LL, Hilal-Dandan R, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 13th ed. New York: McGraw-Hill, 2018, pp. 1203-36.

(Textbook of pharmacology and therapeutics).

FDA. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/212904Orig1s000MultidisciplineR.pdf

(Integrated FDA review of the data on safety and efficacy of tivozanib that formed the basis of its approval, mentions that ALT elevations arose in 30% of patients and were above 5 times ULN in 3.6%, but these rates were similar to those in sorafenib-treated controls [29% and 2.4%], and while there were 4 serious "hepatobiliary" events [2.3%], none were attributed to tivozanib, most being due to hepatic metastases).

Nosov DA, Esteves B, Lipatov ON, Lyulko AA, Anischenko AA, Chacko RT, Doval DC, et al. Antitumor activity and safety of tivozanib (AV-951) in a phase II randomized discontinuation trial in patients with renal cell carcinoma. J Clin Oncol. 2012;30:1678–1685. PubMed PMID: 22493422.

(Among 172 patients with advanced or metastatic renal cell cancer treated with tivozanib or placebo for 12 weeks, progression free survival was increased by tivozanib [10.3 vs 3.3 months], while adverse events included ALT elevations in 29% of patients that were above 5 times ULN in only 1%).

Motzer RJ, Nosov D, Eisen T, Bondarenko I, Lesovoy V, Lipatov O, Tomczak P, et al. Tivozanib versus sorafenib as initial targeted therapy for patients with metastatic renal cell carcinoma: results from a phase III trial. J Clin Oncol. 2013;31:3791–3799. PubMed PMID: 24019545.

(Among 517 patients with metastatic renal cell carcinoma treated with tivozanib or sorafenib, progression free survival was slightly longer with tivozanib [11.9 vs 9.1 months], while adverse events were common in both groups [94% vs 97%] and ALT elevations arose in 28% vs 34% and were above 5 times ULN in 2% vs 4%, and there were no liver related deaths with tivozanib but one with sorafenib).

Rini BI, Pal SK, Escudier BJ, Atkins MB, Hutson TE, Porta C, Verzoni E, et al. Tivozanib versus sorafenib in patients with advanced renal cell carcinoma (TIVO-3): a phase 3, multicentre, randomised, controlled, open-label study. Lancet Oncol. 2020;21:95–104. PubMed PMID: 31810797.

(Among 350 patients with refractory, metastatic renal cell cancer treated with tivozanib or sorafenib, progression free survival was longer with tivozanib [5.9 vs 3.9 months], while adverse event rates were 84% vs 94%, serious adverse event rates 11% vs 10%; no mention of ALT elevations but there were no treatment related deaths).

Albiges L, Barthélémy P, Gross-Goupil M, Negrier S, Needle MN, Escudier B. TiNivo: safety and efficacy of tivozanib-nivolumab combination therapy in patients with metastatic renal cell carcinoma. Ann Oncol. 2021;32:97–102. PubMed PMID: 33010459.

(Among 25 patients with metastatic renal cell carcinoma treated with tivozanib and nivolumab, the objective response rate was 55% and adverse event rate 80%, most frequently hypertension, fatigue and diarrhea, and ALT elevations in 16% which were above 5 times ULN in 1 patient [4%]).

Basso U, Procopio G, Fornarini G, Massari F, Bearz A, Fratino L, Milella M, et al. Safety and efficacy of tivozanib in first-line mRCC: a multicenter compassionate-use study (Meet-Uro 16). Oncology. 2021;99:747–755. PubMed PMID: 34583356.

(Among 64 patients with metastatic renal cell carcinoma treated with tivozanib in a compassionate use protocol, the objective response rate was 34% while the adverse event rate was 92%, the most common side effects being fatigue, hypothyroidism and hypertension, liver toxicity occurring in 4.7%, but no details provided).

Chang E, Weinstock C, Zhang L, Fiero MH, Zhao M, Zahalka E, Ricks TK, et al. FDA approval summary: tivozanib for relapsed or refractory renal cell carcinoma. Clin Cancer Res. 2022;28:441–445. PubMed PMID: 34417198.

(Summary of data on efficacy and safety of tivozanib that led to its FDA approval as therapy of patients with relapsed or refractory advanced renal cell carcinoma after two previous therapies; safety analyses were based upon 6 trials with 1008 treated patients; no mention of hepatotoxicity or ALT elevations).

Heseltine J, Allison J, Wong S, Prasad K, Oong ZC, Wong H, Law A, et al. Clinical outcomes of tivozanib monotherapy as first-line treatment for metastatic renal cell carcinoma: a multicentric UK real-world analysis. Target Oncol. 2023;18:593–599. PubMed PMID: 37285073.

(Among 113 patients with metastatic renal cell carcinoma treated in four cancer centers with tivozanib as a first line therapy, progression free survival was 8.8 months, and the adverse event rate 75% with "deranged liver function tests" in 4%, which were above 5 times ULN in 3%; no details given).