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Dacomitinib

Updated: April 15, 2019.

OVERVIEW

Introduction

Dacomitinib is a multi-kinase receptor inhibitor used in the therapy of cases of non-small cell lung cancer that harbor activating mutations in the epidermal growth factor receptor gene (EGFR). Dacomitinib is associated with high rate of transient serum aminotransferase elevations during therapy but has not been linked to instances of clinically apparent acute liver injury.

Background

Dacomitinib (dak" oh mi' ti nib) is a multi-kinase inhibitor with potent activity against epidermal growth factor receptor 2 genes (HER1, HER2 and HER4), members of the ErbB family of EGFRs. These receptors are often mutated and over expressed in cancer cells, particularly non-small cell lung cancer (NSCLC) and some forms of breast cancer. The mutated EGF tyrosine kinase receptors are constitutively expressed which causes unregulated cell growth and proliferation. By inhibition of this growth factor receptor, dacomitinib blocks the intracellular Ras signaling transduction cascade, which results in inhibition of the malignant cell growth. Highest rates of response to dacomitinib are seen in patients with activating mutations of EGFR in the tumor tissue. Dacomitinib received approval for use in the United States in 2018 for the first line treatment of advanced NSCLC with activating mutations in EGFR (using an FDA-approved test). Dacomitinib is available in tablets of 15, 30 and 45 mg under the brand name Vizimpro. The recommended dose is 45 mg by mouth once daily, with dose modification based upon tolerance, continued until disease progression or intolerable toxicity. Side effects are common and include diarrhea, nausea, vomiting, anorexia, mouth ulcers, conjunctivitis, rash, dry skin, paronychia, hair loss, pruritus and fatigue. Uncommon serious side effects include interstitial lung disease, severe diarrhea or rash and fetal embryonal toxicity.

Hepatotoxicity

In large early clinical trials, elevations in serum aminotransferase levels were common during dacomitinib therapy, arising in 40% of patients treated with standard doses. However, most elevations were transient and asymptomatic, and they rarely led to dose modification or discontinuation. Serum ALT elevations above 5 times the ULN occurred in only 1.4% of patients, these rates being lower than with other EGRF inhibitors such as erlotinib and gefitinib. Serum alkaline phosphatase elevations also occurred but were not common. There were no instances of clinically apparent liver injury with jaundice. However, clinical experience with dacomitinib has been limited.

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

Mechanism of Injury

The cause of the liver injury due to dacomitinib is unknown. Serum enzyme elevations are common during antineoplastic therapy with tyrosine kinase inhibitors, particularly those that target EGFR. The mechanism of injury is unknown but may relate to inhibition of other kinase activities. Dacomitinib is metabolized in the liver largely via CYP 2D6 and is susceptible to drug-drug interactions with other CYP 2D6 substrates.

Outcome and Management

Serum aminotransferase elevations above 5 times the upper limit of normal (if confirmed) should lead to dose interruption. If changes persist, are severe or associated with symptoms or jaundice, or reoccur on restarting, dacomitinib should be discontinued. There have been no published reports of acute liver failure, chronic hepatitis or vanishing bile duct syndrome due to dacomitinib. Patients with liver abnormalities during dacomitinib therapy may tolerate treatment with other EGFR inhibitors without recurrence of severe injury.

Drug Class: Antineoplastic Agents, Protein Kinase Inhibitors

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Dacomitinib – Vizimpro®

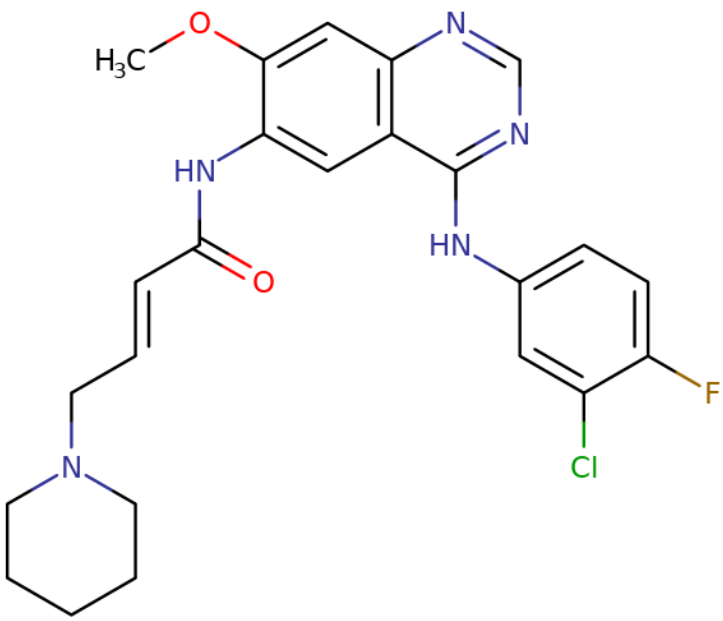
DRUG CLASS

Antineoplastic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Dacomitinib	1110813-31-4	C24-H25-Cl-F-N5-O2	

ANNOTATED BIBLIOGRAPHY

References updated: 15 April 2019

Abbreviations: EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer.

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 receptor inhibitors).

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

(Review of hepatotoxicity of cancer chemotherapeutic agents, discusses gefitinib but not dacomitinib).

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).

Available at: https://www.accessdata.fda.gov/scripts/cder/daf/

(FDA Drug Approvals website that has product labels [package inserts], letters of approval and full FDA scientific review of the new drug application for safety and efficacy).

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Chen X, Pan Y, Zhang S, Chen D, Yang S, Li X, Ma S. Rechallenge with gefitinib following severe drug-induced hepatotoxicity in a patient with advanced non-small cell lung cancer: A case report and literature review. Oncol Lett 2014; 7: 878-80. PubMed PMID: 24527096.

(61 year old woman with NSCLC developed marked ALT elevations 14 months after starting gefitinib [ALT 1,130 U/L], which fell to near normal 10 weeks later and did not increase when gefitinib was restarted one year later).

Yonesaka K, Suzumura T, Tsukuda H, Hasegawa Y, Ozaki T, Sugiura T, Fukuoka M. Erlotinib is a well-tolerated alternate treatment for non-small cell lung cancer in cases of gefitinib-induced hepatotoxicity. Anticancer Res 2014; 34: 5211-5. PubMed PMID: 25202117.

(Among 25 patients with advanced NSCLC treated with gefitinib, 7 developed ALT elevations above 5 times ULN [specific values not given], all of whom then tolerated erlotinib with no or only minor enzyme elevations).

Ramalingam SS, Jänne PA, Mok T, O'Byrne K, Boyer MJ, Von Pawel J, Pluzanski A, et al. Dacomitinib versus erlotinib in patients with advanced-stage, previously treated non-small-cell lung cancer (ARCHER 1009): a randomised, double-blind, phase 3 trial. Lancet Oncol 2014; 15: 1369-78. PubMed PMID: 25439691.

(Among 878 patients with refractory, advanced or metastatic NSCLC treated with dacomitinib vs erlotinib, the median progression free survival was 2.6 months in both groups while adverse events were more frequent with dacomitinib, including diarrhea [11% vs 2%], rash [7% vs 3%], stomatitis [3% vs <1%]; no mention of ALT elevations or hepatotoxicity).

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. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, 49 were attributed to antineoplastic agents [5.5%], 3 of which were attributed to kinase inhibitors [imatinib, lapatinib], but none to erlotinib or gefitinib).

Zenke Y, Umemura S, Sugiyama E, Kirita K, Matsumoto S, Yoh K, Niho S, et al. Successful treatment with afatinib after grade 3 hepatotoxicity induced by both gefitinib and erlotinib in EGFR mutation-positive non-small cell lung cancer. Lung Cancer 2016; 99: 1-3. PubMed PMID: 27565905.

(57 year old man with NSCLC developed ALT elevations 7 weeks after starting gefitinib [bilirubin 2.0 mg/dL, ALT peak 594 U/L], which resolved upon stopping, but he then developed worsening jaundice within a week of starting erlotinib [bilirubin 5.4 mg/dL, ALT normal], and later tolerated afatinib; genetic testing revealed Gilbert syndrome and "poor metabolizer" phenotype of CYP 3A5).

Takeda M, Okamoto I, Nakagawa K. Pooled safety analysis of EGFR-TKI treatment for EGFR mutation-positive non-small cell lung cancer. Lung Cancer 2015; 88: 74-9. PubMed PMID: 25704957.

(A pooled analysis of 21 trials of tyrosine kinase inhibitors of EGFR found higher reported rates of "grade 3" hepatotoxicity with gefitinib [18%] than with erlotinib [5.4%] and afatinib [1.7%], and hepatotoxicity was listed as the cause of drug discontinuation in 25% of cases).

Oh DY, Lee KW, Cho JY, Kang WK, Im SA, Kim JW, Bang YJ. Phase II trial of dacomitinib in patients with HER2-positive gastric cancer. Gastric Cancer 2016; 19: 1095-103. PubMed PMID: 26581547.

(Among 27 patients with advanced gastric cancer and HER-2 mutations treated with dacomitinib, the median progression free survival was 2.1 months and adverse events included skin rash [74%], diarrhea [67%] and fatigue [57%]; no mention of ALT elevations or hepatotoxicity).

Sepúlveda-Sánchez JM, Vaz MÁ, Balañá C, Gil-Gil M, Reynés G, Gallego Ó, Martínez-García M, et al. Phase II trial of dacomitinib, pan-human EGFR tyrosine kinase inhibitor, in recurrent glioblastoma patients with EGFR amplification. Neuro Oncol 2017; 19: 1522-31. PubMed PMID: 28575464.

(Among 49 patients with glioblastoma and EGFR amplification treated with dacomitinib, response rates were less for those with EGFRv111 deletion, while side effects were common including rash [82%] and diarrhea [67%]; one patient had a transient ALT elevation above five times ULN).

Wu YL, Cheng Y, Zhou X, Lee KH, Nakagawa K, Niho S, Tsuji F, et al. Dacomitinib versus gefitinib as first-line treatment for patients with EGFR-mutation-positive non-small-cell lung cancer (ARCHER 1050): a randomised, open-label, phase 3 trial. Lancet Oncol 2017; 18: 1454-66. PubMed PMID: 28958502.

(Among 452 patients with advanced NSCLC treated with dacomitinib or gefitinib for a median duration of 22 months, progression free survival was slightly better with dacomitinib [14.7 vs 9.2 months] but severe adverse events were more frequent, although ALT elevations above 5 times ULN arose in less [1% vs 8%]).

Shirley M. Dacomitinib: first global approval. Drugs 2018; 78: 1947-53. PubMed PMID: 30506139.

(Review of mechanism of action, pharmacology, clinical efficacy and safety of dacomitinib, mentions adverse events of diarrhea [87%], paronychia [62%], acneiform rash [49%], stomatitis [44%] and decreased appetite [31%]; no mention of ALT elevations or hepatotoxicity).