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Anastrozole

Updated: July 25, 2017.

OVERVIEW

Introduction

Anastrozole is a nonsteroidal inhibitor of aromatase which effectively blocks estrogen synthesis in postmenopausal women and is used as therapy of estrogen receptor positive breast cancer. Anastrozole has been associated with a low rate of serum enzyme elevations during therapy and rare instances of clinically apparent liver injury.

Background

Anastrozole (an as' troe zole) is a nonsteroidal inhibitor of aromatase, the enzyme responsible for the conversion of testosterone to estrone (E1) and of androstenedione to estradiol (E2). Highest levels of aromatase are found in the ovary and placenta, which are the major sources of estrogen in premenopausal women. However, aromatase is also found in other tissues, such as liver, kidney, adrenals, brain, muscle and subcutaneous fat where it is also active in producing estrogens, although at low levels. These tissues are the major source of estrogen in postmenopausal women. Inhibitors of aromatase were developed to block the synthesis of estrogen in the peripheral tissues and, thus, as antiestrogen therapy of estrogen receptor positive breast cancer in postmenopausal women. The aromatase inhibitors in current use include letrozole, exemestane and anastrozole. Anastrozole is a nonsteroidal, specific aromatase inhibitor which has little or no effect on adrenal glucocorticoid or mineralocorticoid synthesis. Anastrozole was approved for use in postmenopausal women with breast cancer in the United States in 1995. Anastrozole is available in 1 mg tablets in generic forms and under the brand name Arimidex. Its current indications are as adjuvant therapy in postmenopausal women with hormone responsive breast cancer, as first line therapy of locally invasive or metastatic estrogen receptor positive breast cancer in postmenopausal women, and as adjuvant therapy in postmenopausal women with advanced breast cancer not responsive to tamoxifen. It is typically given in single oral doses of 1 mg daily for up to five years. Common side effects include hot flashes, night sweats, fatigue, dizziness, headache, somnolence, abdominal discomfort, nausea, arthralgias, weight gain and rash. Uncommon, but potentially severe side effects include decrease in bone mineral density, increase in serum cholesterol and increased rate of cardiovascular events.

Hepatotoxicity

Serum enzymes are reported to be elevated in 2% to 4% of women treated with anastrozole, but these elevations are usually mild, asymptomatic and self-limited, rarely requiring dose modification. There have been rare instances of clinically apparent liver injury associated with anastrozole therapy, typically arising within 1 to 4 months of starting treatment and having variable presentations but generally with a hepatocellular or mixed serum enzyme pattern (Case 1). Too few instances have been described in the literature to provide specific

characteristics or clinical phenotype. Immunoallergic features (fever, rash, eosinophilia) were not mentioned in published cases, but low levels of autoantibodies were sometimes found. Recovery is usually rapid once anastrozole is stopped. There have been no cases of acute liver failure, chronic hepatitis or vanishing bile duct syndrome attributed to anastrozole use. Unlike tamoxifen, anastrozole has not been associated with development of fatty liver disease, although some degree of steatosis and steatohepatitis have been mentioned in descriptions of liver biopsies from acute cases. According to the product label, anastrozole has been linked to cases of hypersensitivity reactions and Stevens-Johnson syndrome as well as cases of hepatitis with jaundice.

Likelihood score: C (probable cause of clinically apparent liver injury).

Mechanism of Injury

The liver injury attributed to anastrozole use is probably due to a toxic or immunoallergic intermediate of its metabolism. Anastrozole is metabolized in the liver by the cytochrome P450 system and is a strong inhibitor of CYP 2A6 and to a lesser extent CYP 2C19.

Outcome and Management

Liver injury attributed to anastrozole is usually mild and self-limited, typically a transient, asymptomatic elevation in serum enzymes. Cases of severe hepatitis have been reported in women on anastrozole, but acute liver failure has not. There is little evidence for cross sensitivity to liver injury between anastrozole and tamoxifen or even among the various aromatase inhibitors (which have distinctly different chemical structures).

References to the safety and hepatotoxicity of anastrozole are given below as well as together with those on exemestane and letrozole after the Overview section on Aromatase Inhibitors.

Drug Class: Antineoplastic Agents, Antiestrogens, Aromatase Inhibitors

Other Drugs in the Subclass, Aromatase Inhibitors: Exemestane, Letrozole

CASE REPORT

Case 1. Clinically apparent, acute liver injury due to anastrozole.

[Modified from: Zapata E, Zubiaurre L, Bujanda L, Piérola A. Anastrozole-induced hepatotoxicity. Eur J Gastroenterol Hepatol 2006; 18: 1233-4. PubMed Citation]

An 89 year old postmenopausal woman with estrogen receptor positive breast cancer developed malaise, nausea and vomiting 2 months after starting anastrozole. She had no previous history of liver disease, did not drink alcohol and had no risk factors for viral hepatitis. Before starting anastrozole, serum enzyme levels were reportedly normal. Her other medical conditions included a previous history of bone tuberculosis which was inactive, high blood pressure for which she took diuretics (hydrochlorothiazide), arthritis, vertigo, and urinary incontinence for which she took tolterodine (an anticholinergic). Physical examination revealed jaundice, but no evidence of chronic liver disease or cirrhosis. Laboratory testing showed total bilirubin 3.6 mg/dL (direct 1.5 mg/dL), ALT 410 U/L, AST 255 U/L, alkaline phosphatase 231 U/L, and GGT 364 U/L. Tests for hepatitis A, B and C were negative as were antinuclear and smooth muscle antibody. Ultrasound and CT of the abdomen showed a normal appearing liver with no evidence of biliary obstruction or intrahepatic masses. Anastrozole was stopped and she began to improve. Two weeks later, laboratory tests had returned to normal and she was without symptoms.

Key Points

Medication:	Anastrozole

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Pattern:	Hepatocellular (R=6.5)
Severity:	3+ (jaundice and hospitalization)
Latency:	2 months
Recovery:	2 weeks
Other medications:	Hydrochlorothiazide, tolterodine

Laboratory Values

Time After Starting	Time After Stopping	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	Other
Pre	Pre	Normal	Normal	Normal	Breast cancer diagnosis
8 weeks	0	410	213	3.6	Anastrozole stopped
	3 days	100	133	0.8	Imaging normal
10 weeks	2 weeks	18	94	0.6	Asymptomatic
Normal Values		**<31**	**<104**	**<1.2**	

Comment

The clinical presentation of a mild hepatocellular jaundice arising 2 months after starting anastrozole, the exclusion of other common causes of jaundice, and the prompt improvement on stopping the medication all point to anastrozole induced liver injury.

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Anastrozole – Generic, Arimidex®

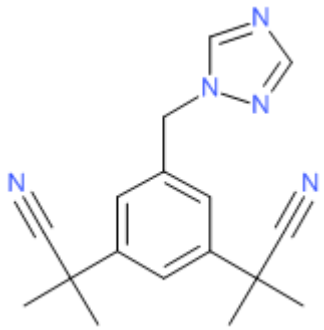
DRUG CLASS

Antineoplastic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Anastrozole	120511-73-1	C17-H19-N5	

ANNOTATED BIBLIOGRAPHY

References updated: 25 July 2017

Zimmerman HJ. Unconventional drugs. Miscellaneous drugs and diagnostic chemicals. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 731-4.

(Expert review of hepatotoxicity published in 1999, before the availability of anastrozole and the aromatase inhibitors).

Chitturi S, Farrell GC. Estrogen receptor antagonists. Adverse effects of hormones and hormone antagonists on the liver. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 610-2.

(Review of hepatotoxicity of tamoxifen mentions that nonalcoholic fatty liver disease is the most common form of liver injury due to tamoxifen which has also been reported to cause peliosis hepatis, acute hepatitis, submassive hepatic necrosis and liver cancer).

Moy B, Lee RJ, Smith M. Anti-estrogen therapy. Natural products in cancer chemotherapy. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 1756-9.

(Textbook of pharmacology and therapeutics).

Carlini P, Papaldo P, Fabi A, Felici A, Ruggeri EM, Milella M, Ciccarese M, et al. Liver toxicity after treatment with gefitinib and anastrozole: drug-drug interactions through cytochrome p450? J Clin Oncol 2006; 24: e60-1. PubMed PMID: 17158530.

(63 year old woman developed ALT elevations [peak 213 U/L] while on gefitinib and anastrozole, which decreased when gefitinib was stopped and increased again when it was restarted).

Zapata E, Zubiaurre L, Bujanda L, Pierola A. Anastrozole-induced hepatotoxicity. Eur J Gastroenterol Hepatol 2006; 18: 1233-4. PubMed PMID: 17033446.

(89 year old woman with breast cancer developed fatigue 2 months after starting anastrozole [bilirubin 1.6 mg/dL, ALT 410 U/L, Alk P 231 U/L], resolving within 2 weeks of stopping).

de la Cruz L, Romero-Vazquez J, Jimenez-Saenz M, Padron JR, Herrerias-Gutierrez JM. Severe acute hepatitis in a patient treated with anastrozole. Lancet 2007; 369 (9555): 23-4. PubMed PMID: 17208628.

(58 year old woman with breast cancer developed jaundice 3 weeks after starting anastrozole [bilirubin 10.9 mg/dL, ALT 2012 U/L, Alk P 4 times ULN], biopsy showing centrolobular necrosis, liver injury resolving rapidly upon stopping, but patient died of complications of emergency ulcer surgery one month later).

Chalasani N, Fontana RJ, Bonkovsky HL, Watkins PB, Davern T, Serrano J, Yang H, Rochon J; Drug Induced Liver Injury Network (DILIN). Causes, clinical features, and outcomes from a prospective study of drug-induced liver injury in the United States. Gastroenterology 2008; 135: 1924-34. PubMed PMID: 18955056.

(Among 300 cases of drug induced liver disease in the US collected between 2004 and 2008, none were attributed to antiestrogens such as exemestane, letrozole, anastrozole or tamoxifen).

Reuben A, Koch DG, Lee WM; Acute Liver Failure Study Group. Drug-induced acute liver failure: results of a U.S. multicenter, prospective study. Hepatology 2010; 52: 2065-76. PubMed PMID: 20949552.

(Among 1198 patients with acute liver failure enrolled in a US prospective study between 1998 and 2007, 133 were attributed to drug induced liver injury, but none were attributed to anastrozole or other antiestrogens).

Dowsett M, Cuzick J, Ingle J, Coates A, Forbes J, Bliss J, Buyse M, et al. Meta-analysis of breast cancer outcomes in adjuvant trials of aromatase inhibitors versus tamoxifen. J Clin Oncol 2010; 28: 509-18. PubMed PMID: 19949017.

(Meta analysis of trials comparing aromatase inhibitors to tamoxifen as adjuvant therapy of breast cancer in postmenopausal women; no discussion of hepatotoxicity or rates of ALT elevations).

Aromatase inhibitors for adjuvant treatment of postmenopausal breast cancer. Med Lett Drugs Ther 2011 13; 53 (1366):47-8. PubMed PMID: 21659970.

(Concise review of the aromatase inhibitors and their role in therapy of breast cancer in postmenopausal women; no discussion of adverse events).

Inno A, Basso M, Vecchio FM, Marsico VA, Cerchiaro E, D'Argento E, Bagalà, Barone C. Anastrozole-related acute hepatitis with autoimmune features: a case report. BMC Gastroenterol 2011; 11: 32. PubMed PMID: 21453541.

(70 year old woman developed fatigue and jaundice 4 months after starting anastrozole [bilirubin 3.5 mg/dL, ALT 1344 U/L, Alk P 640 U/L, ANA 1:80], resolving within 1 month of stopping and not recurring on tamoxifen).

Tomao F, Spinelli G, Vici P, Pisanelli GC, Cascialli G, Frati L, Panici PB, Tomao S. Current role and safety profile of aromatase inhibitors in early breast cancer. Expert Rev Anticancer Ther 2011; 11: 1253-63. PubMed PMID: 21916579.

(Review of efficacy and safety of aromatase inhibitors in early breast cancer; no discussion of hepatotoxicity or ALT elevations).

Goss PE, Ingle JN, Pritchard KI, Ellis MJ, Sledge GW, Budd GT, Rabaglio M, et al. Exemestane versus anastrozole in postmenopausal women with early breast cancer: NCIC CTG MA.27--a randomized controlled phase III trial. J Clin Oncol 2013; 31: 1398-404. PubMed PMID: 23358971.

(Among 7576 women with early breast cancer randomized to anastrozole or exemestane for 5 years, event-free survival was the same while mild bilirubin and ALT elevations were more common with exemestane [1.6% and 1.4%] than anastrozole [0.6% and 0.6%]; no mention of instances of clinically apparent liver injury).

Islam MS, Wright G, Tanner P, Lucas R. A case of anastrazole-related drug-induced autoimmune hepatitis. Clin J Gastroenterol 2014; 7: 414-7. PubMed PMID: 26184021.

(66 year old woman with breast cancer developed abnormal liver tests 6 months after starting anastrazole [bilirubin 2.5 mg/dL, ALT 621 U/L, Alk P 185 U/L, INR 1.4, ANA 1:160] which resolved 3 months after stopping anastrazole, but similar abnormalities arose a year later not on anticancer therapy [bilirubin 2.3 mg/dL, ALT 970 U.L, ANA 1:800] and responded to corticosteroid therapy).

Lin Y, Liu J, Zhang X, Li L, Hu R, Liu J, Deng Y, et al. A prospective, randomized study on hepatotoxicity of anastrozole compared with tamoxifen in women with breast cancer. Cancer Sci 2014; 105: 1182-8. PubMed Citation (Among 353 postmenopausal women with breast cancer followed for 3 years, fatty liver developed in 41% on tamoxifen vs 15% on anastrozole, although rates of ALT elevations were similar in the two groups [any elevations, 16% vs 20%; more than 5 times ULN, <1% in both]).

Lacey R, Evans A. An unusual cause of jaundice in a patient with breast cancer. BMJ Case Rep 2014; 2014. PubMed PMID: 25540208.

(48 year old woman developed jaundice 2 months after starting anastrozole for metastatic breast cancer [bilirubin 33.2 mg/dL, ALT 98 U/L, Alk P 385 U/L, INR 1.9], liver biopsy showing "steatohepatitis" with resolution within 3-6 months of stopping).

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 seen over a ten year period at 8 US medical centers, 7 were attributed to antiestrogens used in cancer chemotherapy including 4 to tamoxifen, 2 exemestane and 1 letrozole, but none were attributed to anastrozole).

Klapko O, Ghoulam E, Jakate S, Eswaran S, Usha L. Anastrozole-induced autoimmune hepatitis: a rare complication of breast cancer therapy. Anticancer Res 2017; 37: 4173-6. PubMed PMID: 28739702.

(71 year old woman with breast cancer developed abnormal liver tests 9 months after starting anastrazole [bilirubin 0.9 mg/dL, ALT 130 U/L, Alk P 95 U/L, ANA 1:1280] despite normal values before treatment, resolving once anastrozole was stopped, but also with prednisone and azathioprine therapy).

Hong N, Yoon HG, Seo DH, Park S, Kim SI, Sohn JH, Rhee Y. Different patterns in the risk of newly developed fatty liver and lipid changes with tamoxifen versus aromatase inhibitors in postmenopausal women with early breast cancer: A propensity score-matched cohort study. Eur J Cancer 2017; 82: 103-14. PubMed PMID: 28651157.

(In a retrospective cohort study of 328 Korean women with breast cancer receiving antiestrogen adjuvant therapy, fatty liver as detected by ultrasound arose in 13 per 100 patient years on tamoxifen versus 8 per 100 on aromatase inhibitors [anastrozole or letrozole], and those on tamoxifen were more likely to progress [42% vs 10%]).