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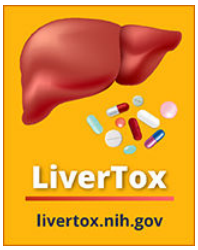


Abiraterone

Updated: March 15, 2023.

OVERVIEW

Introduction

Abiraterone is a steroidal antiandrogen used to treat metastatic, castration-resistant prostate cancer. Abiraterone is associated with an appreciable rate of serum enzyme elevation during therapy and with rare but potentially severe instances of acute liver injury with jaundice.

Background

Abiraterone (a" bir a' ter one) acetate is a semi-synthetic inhibitor of CYP17, a critical enzyme in the pathway of androgen production in the testes and adrenal glands. Abiraterone is used to treat metastatic prostate cancer in men who have undergone castration. The additional inhibition of androgenic steroid synthesis in the adrenals inhibits the growth of the androgen-sensitive prostate cancer cells. Therapy with abiraterone has been shown to prolong relapse-free as well as overall survival in men with metastatic, castration-resistant prostate cancer. Because it acts on another step in the pathway of androgen synthesis and action, abiraterone has been used in combination with agents that block androgen receptors such as enzalutamide and apalutamide, but the combination has not been found to be superior to abiraterone alone. Abiraterone was approved for use in the United States in 2011. It is given in combination with prednisone to prevent hypocorticoidism because abiraterone also inhibits the pathway of cortisol synthesis. In patients who have not undergone orchiectomy, abiraterone should be given in combination with a gonadotropin releasing hormone (GnRH). Abiraterone is available as 250 and 500 mg tablets generically and under the brand name Zytiga. The typical dose is 1000 mg daily in combination with 5 mg of prednisone twice daily. Common side effects include fatigue, nausea, vomiting, diarrhea and abdominal discomfort. Inhibition of CYP17 can also lead to symptoms of mineralocorticoid excess such as hypertension, hypokalemia and fluid retention. Rare but potentially severe adverse events include adrenocortical insufficiency, hypoglycemia in patients with diabetes, increased fractures, embryo-fetal toxicity and hepatotoxicity.

Hepatotoxicity

Serum aminotransferase elevations occur in up to 13% of patients treated with abiraterone compared with 1% to 8% receiving placebo or a comparator drug, but the abnormalities are generally mild, transient and not associated with symptoms or jaundice. ALT elevations above 5 times the upper limit of normal (ULN) occur in 6% of abiraterone treated vs <1% of placebo treated subjects. While clinically apparent liver injury with jaundice was not reported in the preregistration trials of abiraterone, at least 4 cases of acute liver injury with jaundice were reported after its approval and more widespread clinical use. The clinical features of the liver injury have not been well described, but the latency to onset in reported cases ranged from 4 to 8 weeks and the clinical

pattern of illness was acute hepatocellular injury without immune allergic features. Because of the risk of severe acute liver injury with abiraterone therapy, the product label recommends screening for routine liver tests before starting therapy and monitoring of liver tests every 2 weeks for the first 3 months of therapy and monthly thereafter.

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

Mechanism of Injury

The cause of hepatic injury from abiraterone is unknown, but may relate to its mechanism of action in inhibition of CYP17. In addition, abiraterone is metabolized in the liver by the cytochrome P450 system, predominantly CYP 3A4 and 2D6, which may lead to formation of a toxic or immunogenic intermediate. Abiraterone is susceptible to drug-drug interactions with inhibitors, inducers or substrates of the CYP 3A4 or 2D6 microsomal enzymes.

Outcome and Management

The severity of the liver injury linked to abiraterone therapy has been generally mild, consisting of transient and asymptomatic elevations in serum aminotransferase levels. The product label recommends measuring aminotransferase levels every 2 weeks for 3 months and monthly thereafter and stopping therapy if levels rise above 5 times ULN. Abiraterone should not be restarted unless levels return to normal. Any elevation in ALT in the presence of jaundice or symptoms should lead to permanent discontinuation. Abiraterone has not been linked to cases of chronic hepatitis or vanishing bile duct syndrome. There is no information on cross sensitivity to hepatic injury between abiraterone and other antiandrogens.

Drug Class: Antineoplastic Agents, Antiandrogens

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Abiraterone – Generic, Zytiga®

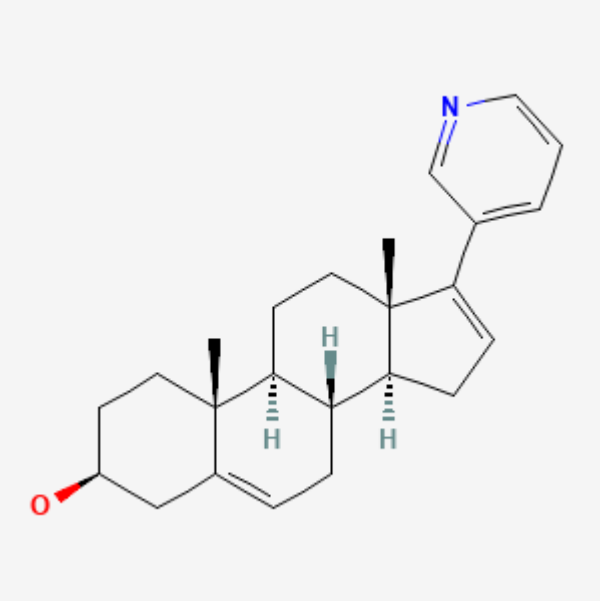
DRUG CLASS

Antineoplastic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Abiraterone	154229-19-3	C24-H31-N-O	

ANNOTATED BIBLIOGRAPHY

References updated: 15 March 2023

Abbreviations: LHRH, luteinizing hormone releasing hormone; PSA, prostate specific-antigen.

Zimmerman HJ. Hepatotoxic effects of oncotherapeutic and immunosuppressive agents. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 673-708.

(Expert review of hepatotoxicity of cancer chemotherapeutic agents published in 1999 before the availability of abiraterone).

DeLeve LD. Cancer chemotherapy. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam, Elsevier, 2013, p. 541-68.

(Review of hepatotoxicity of cancer chemotherapeutic agents; abiraterone is not discussed).

Chabner BA, Bertino J, Cleary J, Ortiz T, Lane A, Supko JG, Ryan DP. Cytotoxic agents. Chemotherapy of neoplastic diseases. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, p. 1698.

(Textbook of pharmacology and therapeutics).

Danila DC, Morris MJ, de Bono JS, Ryan CJ, Denmeade SR, Smith MR, Taplin ME, et al. Phase II multicenter study of abiraterone acetate plus prednisone therapy in patients with docetaxel-treated castration-resistant prostate cancer. J Clin Oncol. 2010;28:1496–501. PubMed PMID: 20159814.

(Among 58 men with castration-resistant, metastatic prostate cancer who had failed docetaxel treatment and were then treated with abiraterone and prednisone, adverse events included fatigue, nausea, vomiting and diarrhea and 3 patients [5%] had ALT elevations, but none were above 3 times ULN).

Ryan CJ, Shah S, Efstathiou E, Smith MR, Taplin ME, Bubley GJ, Logothetis CJ, et al. Phase II study of abiraterone acetate in chemotherapy-naive metastatic castration-resistant prostate cancer displaying bone flare discordant with serologic response. Clin Cancer Res. 2011;17:4854–61. PubMed PMID: 21632851.

(Among 33 patients with castration-resistant prostate cancer treated with abiraterone and prednisone in continuous 28 day cycles, adverse events were common but usually mild; no mention of ALT elevations or hepatotoxicity).

Fizazi K, Scher HI, Molina A, Logothetis CJ, Chi KN, Jones RJ, Staffurth JN, et al. COU-AA-301 Investigators. Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncol. 2012;13:983–92. PubMed PMID: 22995653.

(Among 1195 men with metastatic, castration-resistant prostate cancer enrolled in a controlled trial of abiraterone with prednisone or prednisone alone, both overall and progression free survival were prolonged in the abiraterone arm while side effects were similar in the two groups, including fatigue [9% vs 10%], anemia [8% vs 8%], back pain [7% vs 10%] and abnormal liver tests above 5 times ULN [3.7% vs 3.6%).

Kluetz PG, Ning YM, Maher VE, Zhang L, Tang S, Ghosh D, Aziz R, et al. Abiraterone acetate in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer: U.S. Food and Drug Administration drug approval summary. Clin Cancer Res. 2013;19:6650–6. PubMed PMID: 24150234.

(Summary of clinical results in support of FDA decision to approve abiraterone in combination with prednisone for metastatic, castration-resistant prostate cancer mentions that ALT elevations above 5 times ULN occurred in 6.1% of treated versus 0.7% of control subjects, but that there were no liver related deaths or ALT elevations with jaundice in the preregistration studies [although 2 cases were subsequently reported to the sponsor]).

Rathkopf DE, Smith MR, de Bono JS, Logothetis CJ, Shore ND, de Souza P, Fizazi K, et al. Updated interim efficacy analysis and long-term safety of abiraterone acetate in metastatic castration-resistant prostate cancer patients without prior chemotherapy (COU-AA-302). Eur Urol. 2014;66:815–25. PubMed PMID: 24647231.

(Among 1088 patients with metastatic, castration-resistant prostate cancer treated with abiraterone and prednisone vs prednisone alone [Fizazi 2012] with further follow up, progression-free but not overall survival was significantly better with abiraterone and side effects included fatigue, back pain, arthralgia, peripheral edema, nausea, constipation and diarrhea; ALT elevations above 5 times ULN occurred in 6% vs 1% of patients and was a cause of some early discontinuations for adverse events).

Caffo O, De Giorgi U, Fratino L, Lo Re G, Basso U, D'Angelo A, Donini M, et al. Safety and clinical outcomes of patients treated with abiraterone acetate after docetaxel: results of the Italian Named Patient Programme. BJU Int. 2015;115:764–71. PubMed PMID: 24988879.

(Among 265 Italian patients with metastatic, castration-resistant prostate cancer treated with abiraterone and prednisone, overall mean survival was 17 months and toxicity was rarely dose-limiting; 7 patients [2.6%] developed liver toxicity, but none had ALT values above 5 times ULN).

Sternberg CN, Castellano D, Daugaard G, Géczi L, Hotte SJ, Mainwaring PN, Saad F, et al; Abiraterone Global EAP Investigators. Abiraterone acetate for patients with metastatic castration-resistant prostate cancer progressing after chemotherapy: final analysis of a multicentre, open-label, early-access protocol trial. Lancet Oncol. 2014;15:1263–8. PubMed PMID: 25242048.

(Among 2314 patients with metastatic, castration-resistant prostate cancer who participated in a controlled trial and were then enrolled in an early access program and received abiraterone with prednisone for a median of 6 months, 175 [8%] had "grade 3 liver toxicity" but only 13 [1%] had "grade 4", however, details not provided).

Ryan CJ, Smith MR, Fizazi K, Saad F, Mulders PF, Sternberg CN, Miller K, et al. COU-AA-302 Investigators. Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naive men with

metastatic castration-resistant prostate cancer (COU-AA-302): final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncol. 2015;16:152–60. PubMed PMID: 25601341.

(Among 1088 patients with metastatic, castration-resistant prostate cancer treated with abiraterone and prednisone or prednisone alone, overall survival was slightly longer with abiraterone [34.7 vs 30.3 months] and side effects included mild ALT elevations [13% vs 5%] that were rarely greater than 5 times ULN [0.7% vs 0%]; there were no treatment related deaths).

Houédé N, Beuzeboc P, Gourgou S, Tosi D, Moise L, Gravis G, Delva R, et al. Abiraterone acetate in patients with metastatic castration-resistant prostate cancer: long term outcome of the Temporary Authorization for Use programme in France. BMC Cancer. 2015;15:222. PubMed PMID: 25884302.

(Among 306 patients with metastatic, castration-resistant prostate cancer treated in a French early use program with abiraterone and prednisone, median overall survival was 14.6 months, and 6 patients developed "liver and hepatic" dysfunction; no details provided).

Smith MR, Rathkopf DE, Mulders PF, Carles J, Van Poppel H, Li J, Kheoh T, et al. Efficacy and safety of abiraterone acetate in elderly (75 years or older) chemotherapy naïve patients with metastatic castration resistant prostate cancer. J Urol. 2015;194:1277–84. PubMed PMID: 26151676.

(Among 350 elderly men with metastatic, castration-resistant prostate cancer treated with abiraterone and prednisone vs prednisone alone, both overall and progression-free was higher in the abiraterone treated group and "hepatotoxicity" was greater in the elderly than the younger subjects, being above 5 times ULN in 20.9% vs 9.8% in the treated and 4% and 7.4% in the controls).

Van Praet C, Rottey S, Van Hende F, Pelgrims G, Demey W, Van Aelst F, Wynendaele W, et al. Abiraterone acetate post-docetaxel for metastatic castration-resistant prostate cancer in the Belgian compassionate use program. Urol Oncol. 2016;34:254.

(Among 368 men with metastatic, castration-resistant prostate cancer treated with abiraterone and prednisone in a Belgian compassionate use program, median overall survival was 15 months and side effects include anemia [14%], hypokalemia [7%], fatigue [7%] and liver enzyme elevations [3.5%]; no mention of clinically apparent liver injury).

Sun Y, Zou Q, Sun Z, Li C, Du C, Chen Z, Shan Y, et al. Abiraterone acetate for metastatic castration-resistant prostate cancer after docetaxel failure: A randomized, double-blind, placebo-controlled phase 3 bridging study. Int J Urol. 2016;23:404–11. PubMed PMID: 26879374.

(Among 214 Chinese patients with metastatic, castration-resistant prostate cancer treated with abiraterone and prednisone or prednisone alone, overall survival was greater with abiraterone and adverse events were "generally similar between the two treatment groups"; ALT elevations occurring in 9.8% on abiraterone and 11.3% on placebo).

Fizazi K, Tran N, Fein L, Matsubara N, Rodriguez-Antolin A, Alekseev BY, Özgüroğlu M, et al. LATITUDE Investigators. Abiraterone plus prednisone in metastatic, castration-sensitive prostate cancer. N Engl J Med. 2017;377(4):352–60. PubMed PMID: 28578607.

(Among 1199 men with metastatic, castration sensitive prostate cancer on androgen-deprivation therapy who were treated with abiraterone and prednisone vs placebo, both overall and progression free survival were increased by abiraterone as were serious adverse events [28% vs 24%] and ALT elevations [16% vs 13%] which were above 5 times ULN in 5% vs 1%).

Narita S, Kimura T, Hatakeyama S, Hata K, Yanagisawa T, Maita S, Chiba S, et al. Real-world outcomes and risk stratification in patients with metastatic castration-sensitive prostate cancer treated with upfront abiraterone acetate and docetaxel. Int J Clin Oncol. 2022;27:1477–1486. PubMed PMID: 35748967.

(Among 301 patients with metastatic castration-sensitive prostate cancer treated with abiraterone or docetaxel, the progression free survival was longer with abiraterone but overall survival was similar in the two groups, while severe adverse reactions were more frequent with docetaxel [75% vs 18%], except for ALT elevations which rose to above 5 times ULN in 4.9% of recipients of abiraterone).

Colomba E, Marret G, Baciarello G, Lavaud P, Massard C, Loriot Y, Albiges L, et al. Liver tests increase on abiraterone acetate in men with metastatic prostate cancer: natural history, management and outcome. Eur J Cancer. 2020;129:117–122. PubMed PMID: 32151941.

(Among 25 patients who developed ALT elevations while being treated with abiraterone in a randomized controlled trial [Fizazi et al 2017], peak levels were 1-3 times ULN in 7, 3-5 times ULN in 6, and 5-20 times ULN in 9, resolving in 2 to 14 weeks, half without stopping, 2 of 4 redeveloping ALT elevations upon restarting, but none resulting in jaundice).

Yumiba S, Komori K, Iwanishi T, Koida Y, Kobayashi M, Ono Y. Hinyokika Kiyo. 2017;63:479–482. [A case of fulminant hepatitis after administration of abiraterone acetate]. PubMed PMID: 29232800.

(77 year old Japanese man with prostate cancer developed fatigue 27 days after starting abiraterone [ALT 420 U/L] and developed progressive worsening within days [ALT rising to 1487 U/L, prothrombin index falling to 23%, Alk P and bilirubin levels not provided] and died of liver failure 2 weeks later).

Singh P, Sinha A, Lama Tamang TG, Chandra AB, Huang YJ. Abiraterone-associated fulminant liver failure. Am J Ther. 2018;25:e505–e506. PubMed PMID: 28452846.

(73 year old man with metastatic prostate cancer developed jaundice 7-8 weeks after starting abiraterone [ALT 1800 U/L, AST 1200 U/L, Alk P and bilirubin not provided], with progressive liver failure and death within 2 weeks of onset; in discussion mentions two more cases of clinically apparent liver injury believed to be due to abiraterone reported to the sponsor).

Saad F, Efstathiou E, Attard G, Flaig TW, Franke F, Goodman OB Jr, Oudard S, et al. ACIS Investigators. Apalutamide plus abiraterone acetate and prednisone versus placebo plus abiraterone and prednisone in metastatic, castration-resistant prostate cancer (ACIS): a randomised, placebo-controlled, double-blind, multinational, phase 3 study. Lancet Oncol. 2021;22:1541–1559. PubMed PMID: 34600602.

(Among 982 men with metastatic prostate cancer treated with abiraterone [1000 mg with prednisone] with or without apalutamide [240 mg], radiographic progression free survival was longer with combination therapy [22.6 vs 16.6 months], but overall survival was not different [67% vs 69%] and adverse events were more frequent with the combination, including hypertension [17% vs 10%] and ALT elevations [12% vs 4%], but there were no hepatic deaths or mention of clinically apparent liver injury).

Scailteux LM, Despas F, Balusson F, Campillo-Gimenez B, Mathieu R, Vincendeau S, Happe A, et al. Hospitalization for adverse events under abiraterone or enzalutamide exposure in real-world setting:aA French population-based study on prostate cancer patients. Br J Clin Pharmacol. 2022;88:336–346. PubMed PMID: 34224605.

(Among 11,534 patients newly started on abiraterone or enzalutamide therapy for prostate cancer who were enrolled in the French National Health Insurance System Database between 2013 and 2017, liver test abnormalities were more frequent with abiraterone [17% vs 6%] as were acute kidney injury and atrial fibrillation while "hepatitis" was rare [<0.1%]).

Yanagisawa T, Kimura T, Mori K, Suzuki H, Sano T, Otsuka T, Iwamoto Y, et al. Abiraterone acetate versus nonsteroidal antiandrogen with androgen deprivation therapy for high-risk metastatic hormone-sensitive prostate cancer. Prostate. 2022;82:3–12. PubMed PMID: 34559410.

(Among 312 men with prostate cancer treated with abiraterone [1000 mg] or bicalutamide [80 mg] daily, overall and cancer specific survival were similar in the two groups, but adverse events were more common with abiraterone [27% vs 21%] as was "impaired liver function" [16% vs 2%], although there were no deaths or severe adverse events attributed to liver injury).