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Abiraterone

Updated: July 5, 2017.

OVERVIEW

Introduction

Abiraterone is an antiandrogen used to treat metastatic, castration-resistant prostate cancer. Abiraterone is associated with a not uncommon rate of serum enzyme elevation during therapy, but has not been clearly linked to cases of clinically apparent liver injury with jaundice.

Background

Abiraterone (a" bir a' ter one) acetate is a semi-synthetic steroidal inhibitor of CYP17, a crticial 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 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. Abiraterone was approved for use in the United States in 2011. It is given in combination with prednisone to prevent hypocorticoidism caused by the enzyme inhibition. Abiraterone is available as 250 mg tablets 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.

Hepatotoxicity

Serum aminotransferase elevations occur in up to 13% of patients treated with abiraterone compared with 1% to 8% receiving placebo, 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. Nevertheless, clinically apparent liver injury with jaundice was not reported in the preregistration trials of abiraterone, although such cases including examples of acute liver failure have been reported to the sponsor since its licensure and more widespread use. There have been no publications or descriptions of the clinical features of hepatotoxicity with jaundice associated with abiraterone therapy. The product label recommends monitoring of liver tests during therapy with abiraterone and decreasing the dose in the event of repeat elevations above 2.5 times the ULN and stopping therapy for elevations above 5 times ULN. Therapy should be stopped in the event of ALT elevations accompanied by symptoms of liver injury or jaundice.

Likelihood score: E* (unproven but suspected 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 month and monthly thereafter and stopping therapy if levels rise above 5 times ULN. 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, such as flutamide or bicalutamide.

Drug Class: Antineoplastic Agents, Antiandrogens

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Abiraterone – Zytiga®

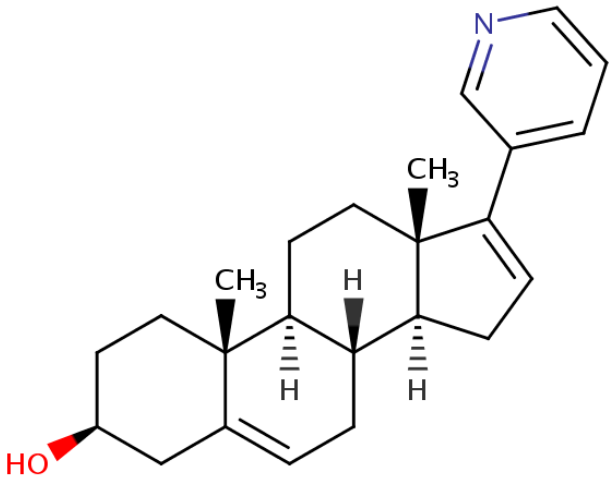
DRUG CLASS

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: 05 July 2017

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. PubMed PMID: 26850781.

(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. *(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* PubMed PMID: 28578607.

as were serious adverse events [28% vs 24%] and ALT elevations [16% vs 13%] which were above 5 times ULN in 5% vs 1%).