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Apalutamide

Updated: April 15, 2019.

OVERVIEW

Introduction

Apalutamide is a nonsteroidal antiandrogen used to treat nonmetastatic castration-resistant prostate cancer. Apalutamide is associated with a low rate of serum enzyme elevation during therapy, but has not been linked to cases of clinically apparent liver injury with jaundice.

Background

Apalutamide (a pa lut' a mide) is a small molecule androgen receptor antagonist which binds to the intracellular receptor and prevents its translocation to the nucleus and subsequent DNA binding, thereby blocking its activity. Therapy with apalutamide lowers residual testosterone levels after surgical castration in men with prostate cancer and has been shown to prolong metastatic free survival in men with castration-resistant prostate cancer with rising levels of prostate-associated antigen (PSA) without measurable metastatic disease. Apalutamide was approved for use in the United States in 2018 and is available as tablets of 60 mg under brand name Erleada. The recommended initial dose is 240 mg daily with subsequent dose reduction for intolerance. Common side effects include symptoms of androgen deficiency including fatigue, diarrhea, nausea, anorexia, weight loss, constipation, joint and muscle pain, hot flushes, headaches, dizziness, and edema. Rare, but potentially serious side effects associated with long term therapy include seizures, osteoporosis, bone fractures and cardiovascular events.

Hepatotoxicity

In prelicensure controlled trials of apalutamide, serum aminotransferase elevations were uncommon and generally transient and mild, not requiring dose modification. Clinically apparent liver injury with jaundice attributable to apalutamide was not reported in the preregistration trials and is not mentioned as an adverse event in the product label. Since the approval and general clinical use of apalutamide, there have been no publications or descriptions of the clinical features of hepatotoxicity with jaundice associated with its use. Other androgen receptor blockers, such as flutamide and bicalutamide, have been linked to rare cases of hepatitis-like liver injury with jaundice that can be severe and even fatal. Such cases have not been described with apalutamide, but clinical experience with its use has been limited. Thus, clinically apparent liver injury due to apalutamide must be rare, if it occurs at all.

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

Mechanism of Injury

The cause of the liver enzyme elevations that occur during apalutamide therapy is unknown. The liver injury from flutamide and bicalutamide is rare and is considered to be idiosyncratic. Apalutamide is extensively metabolized in the liver predominantly by CYP 2C8 and 3A and is an inducer of CYP 3A4. While coadministration of apalutamide with substrates of CYP 3A4 and with modulators of CYP 2C8 and 3A4 may result in drug-drug interactions, the effects are relatively modest.

Outcome and Management

The liver injury linked to apalutamide therapy has been generally mild, consisting of transient and asymptomatic elevations in serum aminotransferase levels and rarely requiring dose modification or discontinuation. Apalutamide has not been linked to cases of acute liver failure, chronic hepatitis or vanishing bile duct syndrome. There is no information on cross sensitivity to hepatic injury between apalutamide and other antiandrogens, such as flutamide, bicalutamide, or abiraterone.

Drug Class: Antineoplastic Agents, Antiandrogens

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Apalutamide – Erleada®

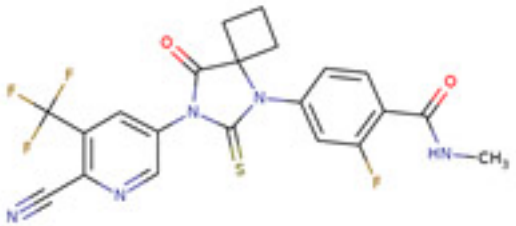
DRUG CLASS

Antineoplastic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Apalutamide	956104-40-8	C21-H15-F4-N5-O2-S	

ANNOTATED BIBLIOGRAPHY

References updated: 15 April 2019

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 apalutamide).

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; apalutamide is not discussed).

Isaacs C, Wellstein A, Riegel AT. Hormones and related agents in the therapy of cancer. Natural products in cancer chemotherapy: hormones and related agents. 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. 1237-48.

(Textbook of pharmacology and therapeutics discusses the androgen receptor antagonists flutamide, bicalutamide, nilutamide and enzalutamide, but not apalutamide).

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; mentions that hepatic laboratory abnormalities were uncommon and the single instance of clinically apparent liver injury with jaundice appeared to be due to progressive hepatic metastases rather than apalutamide toxicity).

(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; mentions that hepatic laboratory abnormalities were uncommon and the single instance of clinically apparent liver injury with jaundice appeared to be due to progressive hepatic metastases rather than apalutamide toxicity).

Tran C, Ouk S, Clegg NJ, Chen Y, Watson PA, Arora V, Wongvipat J, et al. Development of a second-generation antiandrogen for treatment of advanced prostate cancer. Science 2009; 324: 787-90. PubMed PMID: 19359544.

(Description of development of unique antiandrogen molecules that block the translocation of the androgen receptor to the nucleus and the transcriptional activity of the receptor).

Smith MR, Antonarakis ES, Ryan CJ, Berry WR, Shore ND, Liu G, Alumkal JJ, et al. Phase 2 study of the safety and antitumor activity of apalutamide (ARN-509), a potent androgen receptor antagonist, in the high-risk nonmetastatic castration-resistant prostate cancer cohort. Eur Urol 2016; 70: 963-70. PubMed PMID: 27160947.

(Among 51 patients with castration-resistant prostate cancer and rising levels of PSA who were treated with apalutamide [240 mg daily], 89% had a 50% decline in PSA levels within 12 weeks and common side effects were fatigue [61%], diarrhea [43%], nausea [39%], joint and back pain [22%], hot flush [20%] and abdominal pain [18%], and no serious adverse events occurred; no mention of ALT elevations or hepatotoxicity).

Rathkopf DE, Antonarakis ES, Shore ND, Tutrone RF, Alumkal JJ, Ryan CJ, Saleh M, et al. Safety and antitumor activity of apalutamide (ARN-509) in metastatic castration-resistant prostate cancer with and without prior abiraterone acetate and prednisone. Clin Cancer Res 2017; 23: 3544-51. PubMed PMID: 28213364.

(Among 46 men with castration-resistant prostate cancer and rising PSA levels treated with apalutamide [240 mg daily], 88% had at least a 50% decline in PSA levels by 12 weeks, side effects were mostly mild, and there were no treatment-related serious adverse events; no mention of ALT elevations or hepatotoxicity).

Smith MR, Saad F, Chowdhury S, Oudard S, Hadaschik BA, Graff JN, Olmos D, et al.; SPARTAN Investigators. Apalutamide treatment and metastasis-free survival in prostate cancer. N Engl J Med 2018; 378: 1408-18. PubMed PMID: 29420164.

(Among 1207 men with castration-resistant prostate cancer with rising levels of PSA but without detectable metastases in a randomized, placebo controlled trial, median metastasis-free survival was longer with apalutamide than placebo [40.5 vs 16.2 months], and adverse events that were more frequent with apalutamide included fatigue [30% vs 21%], rash [24% vs 6%], weight loss [16% vs 6%], falls [16% vs 9%], fractures [12% vs 7%], hypothyroidism [8% vs 2%] and seizures [0.2% vs none]; no mention of ALT elevations or hepatotoxicity).

Beaver JA, Kluetz PG, Pazdur R. Metastasis-free survival - a new end point in prostate cancer trials. N Engl J Med 2018; 378: 2458-60. PubMed PMID: 29949489.

(Editorial from FDA on the implications of the approval of apalutamide and application of metastasis-free survival [rather than overall survival] as an end-point in assessing efficacy of new agents for prostate cancer, stressing the importance of balancing benefit with safety and risk of adverse events).

Al-Salama ZT. Apalutamide: first global approval. Drugs 2018; 78: 699-705. PubMed PMID: 29626324.

(Review of the structure, mechanism of action, history of development, clinical efficacy and safety of apalutamide; mentions that overall and serious adverse event rates were similar in apalutamide- and placebo-treated subjects; no mention of ALT elevations or hepatotoxicity).

Apalutamide (Erleada) for prostate cancer. Med Lett Drugs Ther 2018; 60 (1551): e124-e125. PubMed PMID: 30036351.

(Concise review of the efficacy, safety and costs of apalutamide shortly after its approval in the US mentions side effects reported by Smith et al. [2018], but does not mention hepatotoxicity or ALT elevations).