ZYTIGA® (abiraterone acetate)
ZYTIGA - QT Prolongation and Torsades de Pointes

SUMMARY

- ZYTIGA may cause hypertension, hypokalemia, and fluid retention as a consequence of increased mineralocorticoid levels resulting from cytochrome P450 (CYP)17 inhibition and is indicated for use in combination with prednisone/prednisolone.[1] Closely monitor patients whose underlying medical conditions might be compromised by increases in blood pressure, hypokalemia, or fluid retention, such as those with heart failure, recent myocardial infarction, cardiovascular disease, or ventricular arrhythmia. Control hypertension and correct hypokalemia before treatment. Monitor blood pressure, serum potassium and symptoms of fluid retention at least monthly. In postmarketing experience, QT prolongation and Torsades de Pointes have been observed in patients who develop hypokalemia while taking ZYTIGA.[2]
- The safety of ZYTIGA in patients with left ventricular ejection fraction (LVEF) <50% or New York Heart Association (NYHA) Class III or intravenous (IV) heart failure (in COU-AA-301) or NYHA Class II to IV heart failure (in COU-AA-302 and LATITUDE) has not been established because these patients were excluded from these randomized clinical trials.[1,3,4]
- In a phase 1b, open-label, single-arm, multicenter study conducted to assess the effect of ZYTIGA and prednisone on QT interval, 33 patients with metastatic castration-resistant prostate cancer (mCRPC) received ZYTIGA 1,000 mg once daily in combination with prednisone 5 mg orally twice daily. No patient had a LVEF <50%. Assessments up to cycle 2, day 2 showed the upper bound of the 2-sided 90% confidence interval (CI) for the mean baseline-adjusted QT interval corrected using Fridericia's formula (QTcF) change was <10 milliseconds (ms). No patient discontinued therapy due to corrected QT interval (QTc) prolongation or adverse event (AE). No apparent relationship between change in QTcF and abiraterone plasma concentrations was observed.[5]
- QT prolongation and Torsades de Pointes have been observed in patients who develop hypokalemia while taking ZYTIGA.[6-11]
- Real-world studies have been published comparing hospitalization rate among patients treated with ZYTIGA vs enzalutamide that included incidence of QT prolongation and Torsades de Pointes.[12,13]

CLINICAL DATA

QT Prolongation and/or Torsades de Pointes

Phase 1/2 Studies

In a phase 1b, open-label, single-arm, multicenter study conducted to assess the effect of ZYTIGA and prednisone on QT interval, 33 patients with mCRPC received ZYTIGA 1,000 mg once daily in combination with prednisone 5 mg orally twice daily. No patient had a LVEF <50%. Assessments up to cycle 2, day 2 showed the upper bound of the 2-sided 90% CI for the mean baseline-adjusted QTcF change was <10 ms. No patient discontinued therapy due to QTc prolongation or AEs. No apparent relationship between change in QTcF and abiraterone plasma concentrations was observed.[5]

Additionally, in a retrospective analysis of electrocardiogram (ECG) data from 3 phase 1/2, single-arm, open-label studies (N=124), no patients had QTc prolongation after administration of ZYTIGA plus prednisone.[14]

Case Reports

Rodieux et al (2015)[6] described a 74-year-old patient with hypertension, diabetes, anxiety disorder, and mCRPC who had life-threatening Torsade de Pointes associated with a prolonged QTc interval. The patient presented with cardiac arrest. Lab results included severe hypokalemia (2.5 milliequivalent [mEq]/L) and mild hypocalcemia (4.1 mEq/L). The patient was taking ZYTIGA, in addition to other medications, and was found to have poor adherence to prednisone. ZYTIGA was discontinued during the admission. The patient's serum potassium returned to normal by day 2 and the QTc interval gradually decreased by day 6. The patient was discharged 2 weeks later.

Khan et al (2016)[7] described a 77-year-old patient with ischemic heart disease, previous coronary artery bypass grafting, atrial fibrillation, and mCRPC who had recurrent Torsades de Pointes due to hypokalemia (2.7 mmol/L) with a prolonged QTc interval. The patient was taking ZYTIGA plus prednisone, in addition to other medications. ZYTIGA was discontinued during admission, and the patient was discharged after remaining stable. The patient's electrolytes remained normal at clinic follow-up 1 month later.

Morales et al (2021)[8] described a 70-year-old patient with hyperlipidemia, hypertension, and mCRPC who presented with recurrent syncope without prodrome. ECG revealed frequent ventricular ectopy, non-sustained episodes of Torsade de Pointes, severe hypomagnesemia (0.8 mg/dL), and hypokalemia (2.4 mEq/L). Additional testing revealed mild coronary artery disease and moderately depressed LVEF. After electrolyte disturbances were corrected, the QT interval normalized. The patient was taking ZYTIGA, in addition to other medications. ZYTIGA was discontinued during the admission, and the patient returned to baseline and was discharged. Of note, the patient was not receiving prednisone at the time of admission.

Riad et al (2021)[9] described a 78-year-old man with hypertension and mCRPC who presented with progressive generalized weakness and shortness of breath. Laboratory results revealed a potassium level of 2.2 mmol/L, magnesium level of 2.4 mg/dL, and normal kidney and hepatic functions. The initial ECG showed atrial fibrillation with a rapid ventricular rate, frequent premature ventricular contractions, and a prolonged QTc (634 ms). Overnight, the patient developed multiple episodes of Torsade de Pointes, became pulseless, and underwent advanced cardiac life support, including defibrillation. The patient was taking ZYTIGA in addition to other medications. The patient was started on IV lidocaine and dopamine infusion to augment the heart rate and assist in shortening the QTc. A slight improvement in potassium level (2.8 mmol/L) was observed despite a total of 220 mEq of IV potassium chloride. The patient received spironolactone and amiloride for urinary potassium reabsorption, in addition to hydrocortisone, to reduce the effect of ZYTIGA on increasing mineralocorticoid synthesis. After this, his potassium level normalized. Upon discharge, the patient was advised to discontinue ZYTIGA indefinitely and follow-up with his oncologist for further evaluation and management of cancer. At 3 months follow-up after discharge, the patient was symptomatically well and had normal electrolyte levels after discontinuation of ZYTIGA.

McBride et al (2021)[10] analyzed postmarketing reports of QT prolongation and/or Torsades de Pointes associated with ZYTIGA. Searches of the FDA Adverse Event Reporting System (FAERS) and literature were conducted for all cases of QT prolongation or Torsades de Pointes with ZYTIGA use from April 28, 2011, to May 1, 2019. The details of the 9 cases identified are presented in Table: Postmarketing Cases of QT Prolongation/TdP Reported with ZYTIGA. Hypokalemia was observed with Common Terminology Criteria for Adverse Events (CTCAE) grade 3 or grade 4 QTc prolongation in 6 cases. Two of the cases with hypokalemia were not taking concomitant corticosteroids.

Postmarketing Cases of QT Prolongation/TdP Reported with ZYTIGA[10]

Case	Age (years)	Time to onset (days)	Peak QTc[a] (ms)	TdP	Lowest Potassium (mEq/L)	Corticosteroid	QT Prolonging Medications	Clinical Outcome	Other
1[6]	74	180	620	Y	2.5	N	None	Hospitalization, Resolved	HTN, DM, "mild hypocalcemia", Mg normal day 1
2[7]	77	180	650	Y	2.7	Y	Goserelin	Hospitalization, Resolving	Prior CABG, AF, Mg, Ca normal
3	79	41	NR	Y	2.6	NR	Leuprolide	Hospitalization, Died 6 days later[b]	CAD, HTN
4	84	233	NR	Y	"hypopotassemia"	NR	None	Hospitalization, Resolved	Concomitant captopril suggests HTN or HF
5	66	NR	NR	Y	"hypokalemia"	Y	NR	Hospitalization, NR	HTN, DM, hyperlipidemia, "hypomagnesemia, hyponatremia" at time of admission
6	79	NR	629	N	2.7	Y	Triptorelin	Hospitalization, NR	Concurrent HF, pneumonia, Mg low day 1
7	71	86	"prolonged QT"	N	NR	Y	Leuprolide	Hospitalization, Resolved	HF, HTN, arrythmia
8	82	4	"prolonged QT"	N	NR	N	None	NR	HTN
9	66	505	"CTCAE Grade 3"	N	4.0	Y	Possible leuprolide[c]	Hospitalization, Resolved	"former smoker"

Abbreviations: AF, atrial fibrillation; Ca, calcium; CABG, coronary artery bypass graft; CAD, coronary artery disease; CTCAE, Common Terminology Criteria for Adverse Events; DM, diabetes mellitus; HF, heart failure; HTN, hypertension; mEq, milliequivalent; Mg, magnesium; ms, milliseconds; N, no; NR, not reported; QTc, corrected QT interval; TdP, Torsades de Pointes; Y, yes.

[a]Method used for calculating QTc was not specified by reporters. CTCAE grades of QTc interval prolonged start with Grade 1, QTc 450-480 ms.

[b]Reported cause of death was cardiac arrest. The patient experienced fatal cardiac arrest 6 days after an episode of TdP with severe hypokalemia.

[c]Case narrative reported a history of leuprolide therapy but did not clearly document concomitant leuprolide with ZYTIGA.

Lee et al (2022)[11] described a 61-year-old patient with a history of mCRPC who presented with a sudden episode of syncope while standing. ECG revealed sinus bradycardia with the presence of U-waves and a prolonged QT interval. The patient had multiple episodes of nonsustained ventricular tachycardia upon arrival at the emergency room, which rapidly progressed to Torsades de Pointes. Laboratory tests revelated severe hypokalemia (2.4 mEq/L). The patient was taking ZYTIGA, in addition to other medications. Initially, potassium was repleted with 60 mEq of oral potassium, followed by 40 mEq of IV potassium over 4 hours. Potassium levels were maintained above 4 mEq/L with additional 140 mEq IV potassium (final 4.6 mEq/L). ZYTIGA and prednisone were restarted upon discharge as hypokalemia was a preventable cause of ventricular arrhythmia. The patient continued daily potassium supplementation of 40 mEq and had no recurrence of ventricular arrhythmias or syncope, with the maintenance of normal potassium levels.

LITERATURE SEARCH

A literature search of MEDLINE®, Embase®, BIOSIS Previews®, and Derwent Drug File (and/or other resources, including internal/external databases) was conducted on 17 May 2024.

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