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Case Report

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LOW-DOSE ENZALUTAMIDE AS SECOND-LINE HORMONE THERAPY IN CASTRATION-RESISTANT PROSTATE CANCER - TWO CASES

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ABSTRACT

Enzalutamide at a recommended dosage of 160 mg / day is approved for the treatment of metastatic castration-resistant prostate cancer (mCRPC) by improving overall survival in chemo-naive patients but also in those who progressed under docetaxel. It is also indicated in locally advanced disease. We report two cases of good tolerance and clinical remission with low-dose enzalutamide.

KEYWORDS: Enzalutamide at a recommended with low-dose enzalutamide.

INTRODUCTION

Enzalutamide is approved in the treatment of metastatic castration-resistant prostate cancer (mCRPC). It improves overall survival in chemo-naive mCRPC patients and in patients who progress on docetaxel (PREVAIL and AFFIRM trials, respectively).[1,2] It is also indicated in non-metastatic chemotherapy-naive patients (STRIVE).[3] and mCRPC (STRIVE and TERRAIN).[3,4]

All of these studies were carried out on a dosage of 160 mg / day.

We report two (2) cases of patients treated with a half-dose and a quarter-dose.

Case 1:
A 79-year-old patient was followed since 1997 for a prostatic adenocarcinoma, clinical stage T2cN0M0 with an initial PSA 43 ng / ml, Gleason 5. The patient had a history of diabetes, hypertension, meningioma in 2007 (treated surgically and then with Keppra 250 mg until 2015), and pulmonary embolism. His prostate cancer was initially treated with prostate radiotherapy to a dose of 70 Gy. He received hormone therapy with bicalutamide 50 mg, triptorelin, and then leuprorelin in 2001.

In 2015, the patient returned with a progression of his PSA. Workup with a whole-body and bone scan found no recurrence or distant metastasis. The PSA progressed from 11 ng/ml on 5/19/2015 to 27.77 on 9/9/2015 and 32.74 on 10/15/2015. The testosterone was 0.35 ng/ml. Clinically, he was asymptomatic, and the digital rectal examination found a prostate 2.5 cm in size with induration of the right apex. A choline-PET scan was done, showing 2 prostatic hypermetabolic foci. Local recurrence was confirmed by prostate biopsy that showed a Gleason 9 adenocarcinoma with peripheral nerve and capsular invasion. Bilateral orchiectomy was performed. The PSA continued to rise and was 53.30 ng/ml by the end of 2016. Clinically, the patient presented with bilateral gynecomastia and a 3-cm prostate induration of the right apex with irregular edges.

In consideration of the patient's age and medical history, enzalutamide was prescribed in December 2016 at a dosage of 80 mg daily, instead of 160 mg, with vitamin D supplementation. The PSA was 58.87 ng / ml.

At three months, the PSA decreased to 3.030 ng / ml. Now, at nine months, the PSA is at 0.934 ng / ml. The patient remains symptom-free and is in clinical remission with a soft prostate of 2 cm of size on digital rectal examination.

Case 2:
An 84-year-old patient with a prostate adenocarcinoma, pT3N0 Gleason 6 (3+3), was treated in 1997 by radical prostatectomy. He received adjuvant radiotherapy of 70 Gy to the prostatic loge and, thereafter, bilateral orchiectomy in 2001 for biological relapse. The PSA increased in 2009, for which the patient received intermittent hormone therapy with bicalutamide 50 mg daily.

The follow-up CT imaging in 2015 showed lombo-aortic lymph node metastasis. The PSA was 20.15 ng / ml, then

21.47 ng/ml while the patient was still receiving bicalutamide.

Lab testing showed increased gamma-GT at 134 IU /I.

Clinically, he had urinary symptoms.

Low-dose enzalutamide 40 mg / day was prescribed. At three months, the PSA decreased to 8.07 ng / ml, at 6 months 3.46 ng / ml, at 9 months 2.40 ng/ml, at 12 months 1.28 ng / ml and now, at 16 months, 0.722 ng / ml.

Clinically he has bilateral gynecomastia, but otherwise the patient is symptom-free.

DISCUSSION

Enzalutamide is rapidly absorbed, with a peak concentration reached after 1-2 hours.[5]

The median peak plasma concentration is reached after 132 and 96 hours.

Dose proportional pharmacokinetics were observed at 40 to 360 mg.[6]

The bioavailability remains unknown because the administration is done orally.

Enzalutamide is widely distributed in tissues and strongly binds to proteins (approximately 97-98%), resulting in an apparent oral distribution volume (Vd / F) of approximately 110 L.[5] The active metabolite N-desmethyl enzalutamide is also bound to proteins (95%).[5]

The two main metabolites in circulation are active N-desmethyl enzalutamide (M2), which is as active as enzalutamide in vitro, and the inactive metabolite of carboxylic acid (M1).[5,6] The steady-state concentrations are similar for enzalutamide and its active metabolite N-desmethyl enzalutamide, and thus both substances contribute to pharmacological activity.[5,6]

Enzalutamide acts on tumor proliferation and induces cell death of prostate cancer cells in vitro and decreases tumor volume in a xenograft of prostate cancer in mice.

In a dose escalation study, the half-life in 140 mCRPC patients was 5.8 days, steady state was reached by day 28, accumulation was 8.3-fold, the exposure was approximately dose-proportional at 30-360 mg / day, and intersubjective variability was B30%.[7]

The approved dose in phase IIIb is 160 mg (4 x 40 mg capsules) administered orally once a day.

The most common side effects are asthenia / fatigue, hot flushes, headache and hypertension. Other important effects include falls, non-pathological fractures, cognitive impairment, and neutropenia.

In a hepatic impairment study, the AUC of the sum of enzalutamide and N-desmethyl enzalutamide was similar in men with mild (n = 6) or moderate (n = 8) hepatic impairment (grade A and B from Child-Pugh) and men with normal liver function (n = 14).

In phase III clinical trials, 7 (0.4) of the 1671 patients treated with 160 mg of enzalutamide experienced seizures versus a single placebo (0.1%). The dose appears to be an important predictor of the risk of seizures. In both phase III studies, patients with a history of seizures or risk factors for seizures were excluded.

Little is known about the efficacy of low-dose enzalutamide. Mark. A et al. reported a good clinical and laboratory response in a case of dose reduction of 80 mg / day in 2 weeks and shale 120 mg / day in a patient with a history of trigeminal neuralgia and hypertension.[10] Sato et al., reported a patient initially treated with enzalutamide at the dosage of 160 mg / day who presented with thrombocytopenia, which led to a reduction in dosage to 80 mg / day without adverse impact on biological response and without relapse of thrombocytopenia.[11]

We were concerned with our patients' risk factors and frailty. Hence, we started empirically with low-dose enzalutamide and continued. The clinical tolerance and biological response is excellent.

CONCLUSION

Pending a prospective clinical trial, we argue that low-dose enzalutamide might be warranted in elderly patients to prevent the risk of severe side effects.

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