

Long term response with abiraterone without lhrh analogs in metastatic castration resistant prostate cancer

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Abstract

Main findings: A clinically localized Gleason score 6 adenocarcinoma was diagnosed to a 59 year-old man, surgically treated with successful oncologic outcomes. However, disease progression led to a diagnosis of metastatic castration resistant prostate cancer (mCRPC) 11 years later, treated with Abiraterone with a prostate-specific antigen (PSA) response of 32 months.

The particular characteristic of this case is that Abiraterone was used without luteinizing hormone releasing hormone (LHRH) analogs and the clinical and biochemical response was prolonged.

Abbreviations: CRPC: Castration Resistant Prostate Cancer; mCRPC: metastatic Castration Resistant Prostate Cancer; PSA: Prostate-specific Antigen; LHRH: Luteinizing Hormone Releasing Hormone; LH: Luteinizing Hormone; ADT: Androgen Deprivation Therapy; CYP 17: Enzyme 17a- Hidroxilase/C17,20-Liase; ASCO: American Society of Clinical Oncology

Case hypothesis

Abiraterone blocks cytochrome P450 c17, thereby inhibiting androgen synthesis by the adrenal glands, testes and within the prostate tumor [1-4].

Two studies led to the approval of Abiraterone, COU AA 301 showed prolonged survival after docetaxel treatment [5] and COU AA 302, in chemotherapy-naive patients [6]. In both, Abiraterone was associated with LHRH agonists, setting the standard for its use together.

The rationale for this association is that luteinizing hormone (LH) must be blocked because fall of testosterone would cause a rise in LH production, with a testosterone increase and a *flare effect* [7]. However, such effect has not been seen in castrated patients [8].

Promising future implications

The use of Abiraterone alone, with successful outcomes in managing mCRPC supports an important line of research that is already being investigated in clinical trials [9,10] and might eventually change the current *state of the art* for mCRPC.

Scenario

A 59-year old patient with a prostate-specific antigen (PSA) value of 12 ng/ml, was diagnosed in 2002 with a localized, intermediate-risk prostate cancer according to D'Amico risk stratification [11]. He was treated with radical prostatectomy and standard lymphadenectomy, with organ-confined disease at final pathology and a 5-year complete response without evidence of disease recurrence. However, in 2007 PSA rose, androgen deprivation therapy (ADT) was initiated, bone

metastases appeared, metastatic disease was controlled for more than 3 years including secondary hormonal manipulations (antiandrogen withdrawal, use of LHRH antagonists) and finally metastatic castration resistant prostate cancer (mCRPC) was diagnosed in 2013 and treated with Abiraterone. Right hip was irradiated due to symptomatic bone metastasis. Osteonecrosis of the jaw developed related to the use of zoledronic acid and was successfully treated, and a 32-month PSA response to Abiraterone was reported, associated with Prednisone but without the use of concomitant luteinizing hormone releasing hormone (LHRH) agonists. This occurred because the patients' medical insurance company did not accept the prescription of Abiraterone and LHRH analogs together. The treatment was well tolerated by the patient, who already had renal insufficiency and heart failure. PSA values were below 1 ng/ml for 2 years and started to rise afterwards, reaching 12 ng/ml in March 2016, surpassing the value of PSA when Abiraterone treatment was initiated (8 ng/ml). While the patient being treated, neither urinary complaints nor metastases-related symptoms developed.

The patient is currently undergoing re-staging imaging studies and was sent to Clinical Oncology Department for further treatment.

Case hypothesis and rational

Prostate cancer is an androgen-dependent disease that generally responds to surgical or medical castration, however, after a variable period of time, cancer is reactivated in certain cases despite castration levels of testosterone, shifting to the stage of CRPC [12]. Progression to this final stage is still driven by androgens, involving different mechanisms of resistance. Among these pathways is the up-regulation of androgen biosynthesis enzymes, producing an increase in intratumoral androgen concentrations [13-15].

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Abiraterone is an androgen-biosynthesis inhibitor, selectively blocking the enzyme 17 α - hidroxilase/C17,20-liase (CYP17), a critical enzyme in testosterone synthesis, necessary for androgen synthesis in testicular, adrenal and prostatic tumour tissue, since it favours the conversion of pregnenolone and progesterone to dehydroepiandrosterone and androstenedione [16].

The current *state of the art* for managing metastatic CRPC indicates that Abiraterone must be given together with LHRH agonists [17-19], since this is how the drug was used in clinical trials that led to its approval [5,6].

The rationale for this association is that after LHRH agonist administration, LH peaks at about three times the baseline level at 24 hours. Testosterone rise is delayed, with a peak reached at approximately day 3, falling to pretreatment levels by day 7. Ultimately, castrate levels are achieved by 3 weeks following initiation of therapy. Blockade of clinical flare can be accomplished with different agents such as Cyproterone, Diethylstilbestrol, Flutamide, or Nilutamide [7]. Although not often used, treatment with Ketoconazole will also prevent flare [20].

Ketoconazole, an imidazole antifungal agent, inhibits many cytochrome P450 enzymes including CYP17A1, suppressing adrenal and intratumoral steroidogenesis by inhibiting the conversion of cholesterol to pregnenolone. It has been used after ADT failure for more than 30 years with PSA response rates and time to progression of 20–75% and 3–10 months, respectively. A study published in 2014, compared Ketoconazole with Abiraterone in post Docetaxel mCRPC. PSA response, progression free survival, radiological PFS, overall survival and treatment interruption due to severe adverse events were analyzed. In all the parameters compared Abiraterone was superior, with less toxicity [21].

This analysis brings the issue of the real need of LHRH analogs together with Abiraterone. If Ketoconazole has been used to avoid the flare, and Abiraterone is superior to Ketoconazole, isn't it enough to use Abiraterone monotherapy?

In the case presented Abiraterone was administered with Prednisone but without associated LHRH analogs. There are very few reports about the use of Abiraterone without LHRH analogs, anyway, it seems to maintain efficacy [8].

Two clinical trials evaluating Abiraterone monotherapy are ongoing. One of them is a phase 2, randomized, 3-arm study of Abiraterone alone, Abiraterone plus Degarelix, and Degarelix alone for patients with prostate cancer with a rising PSA or a rising PSA and nodal disease following radical prostatectomy. The primary outcomes are progression-free survival and soft tissue (lymph nodes) complete response. This interventional study is sponsored by Memorial Sloan Kettering Cancer Center and is still recruiting patients [9].

The second study is SPARE trial. It is a phase 2 multicenter, randomized, open-label study with two arms, Abiraterone plus Prednisone plus LHRH-therapy versus Abiraterone plus Prednisone. The primary outcome is radiographic-progression-free survival. It is a German study, some sites are still recruiting and others already closed [10].

Besides maintaining efficacy, Abiraterone monotherapy spares the patient a series of well-known adverse events related to ADT use: cardiovascular morbidity, metabolic syndrome, fatigue, sarcopenia and muscular weakness, altered body composition, osteoporosis and bone fractures, arterial stiffness, cognitive decline, loss of libido and sexual

disfunction [22].

American Society of Clinical Oncology (ASCO) published in 2014 recommendations on systemic therapies for metastatic CRPC patients, based on clinical benefit, harm, evidence strength and recommendation strength. This document, regarding continuous ADT, states that it should be continued indefinitely regardless of additional therapies. However, it is recognized that clinical benefit is moderate, harm is moderate, evidence strength is weak and recommendation strength is moderate. They declare that in incurable metastatic prostate cancer patients, the goal of treatment is to provide the best possible quality of life. In this age group, additional chronic conditions are common, adding complexity to the management of these patients. Among these more frequent diseases are hypertension, hyperlipidemia, diabetes, ischemic heart disease, anemia, depression, heart failure, arthritis, chronic obstructive pulmonary disease and chronic kidney disease [23]. ADT has a direct negative impact on most of these diseases affecting prostate cancer patients [12].

Our reported 32-month response was only achieved by few of the patients in the COU AA 302 trial and none of the COU AA 301, the pivotal trials that led to Abiraterone approval [5,6]. In fact, the longer response reported in these studies was 34.9 months (maximum rank of response to treatment in an interim analysis of the COU AA 302 published in 2014) [24] and these results were obtained with associated LHRH analogs use.

The outcomes presented in this case report and the cited ongoing trials present a situation that was not thought a few years ago. If confirmed by further scientific evidence, not using a LHRH analog in this clinical scenario would diminish toxicity as well as costs of treatment, maintaining good oncologic outcomes.

Discussion and future perspectives

Available evidence has set the standard of care for mCRPC associating Abiraterone and LHRH analogs [17-19].

However, recent publications are challenging this gold-standard and Abiraterone is being used in clinical trials and few case reports, without LHRH agonists [8-10] and it seems that the effect of the drug is enough to maintain androgen blockade and allowing disease control, without compromising patient's oncologic status and general health. Besides, studies prove that Abiraterone is superior to Ketoconazole [21], and the latter has historically been used to avoid testosterone flare [20].

Even more, the withdrawal of LHRH analogs would spare the patients many drug related drawbacks and lower the costs of treatment.

Some questions arise: are LHRH agonists always necessary for mCRPC patients treated with Abiraterone? Could this monotherapy maintain its efficacy at long term? Might it be possible to challenge the *state of the art* for treating mCRPC patients?

Results of ongoing trials are expected, as well as more scientific evidence, but it looks like Abiraterone monotherapy treatment is here to stay.

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