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Review Article

METABOLISM OF ABIRATERONE IN THE TREATMENT OF CASTRATION RESISTANT ADVANCED PROSTATE CANCER

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ABSTRACT

Prostate cancer is the most common type of malignancy in men and is the second leading cause of cancer-related death. Although the treatment modalities of castration resistant advanced prostate cancer are changing rapidly, managing every patient needs an individualized approach. Abiraterone has been approved for advanced prostate cancer and has showed promising results. However, there are still number of cases which show relative tolerance to abiraterone therapy as well as other antiandrogens. Current clinical challenge is to better understand the correlation of abiraterone drug metabolism with the mechanisms of the disease progression and developments of resistance to targeted therapies. We summarize clinical trials on the metabolic properties of Abiraterone and their clinical significance in the treatment of castration resistant advanced prostate cancer.

INTRODUCTION

Advanced Prostate cancer:

Prostate cancer is one of the most common cancers in men. It is estimated that 1 in 6 US men will develop prostate cancer during their lifetime and that over 70% of these cases will be among men older than age 65[1]. Advanced prostate cancer occurs when a tumor that develops in the prostate gland spreads outside the gland. The most common sites of prostate cancer spread are to the lymph nodes and bones. The current evidence suggests that patients with significant risk of progressive disease and/or death from prostate cancer should be included in the definition and that any patient with cancer outside the prostate capsule with disease stages as low as T3/N0/M0 clearly has “advanced” disease and should be treated accordingly.[2]

After widespread use of prostate-specific antigen screening programs the occurrence of metastatic prostate cancer rates subsequently declined. However, taking into account the relatively high occurrence of the cancer type itself, management of Advanced prostate cancer is still a challenge for clinicians.

Castration resistant prostate cancer (CRPC):

The hormone dependence of prostate cancer was first discovered by the urologist Charles Huggins back in 1941. Huggins was awarded the Nobel Prize in Physiology and Medicine in 1966 for his contribution to the treatment of prostate cancer. On this basis, Huggins and Hodges introduced surgical castration and the administration of estrogens to decrease the serum androgen levels in patients with advanced prostate cancer, which is now called androgen deprivation therapy.

Castration resistance is defined as the progression of disease after surgical castration, and it precedes hormone resistance, which is defined as the progression of disease despite whichever hormonal manipulation is added to castration. The current criteria to define the progression of PCa after castration is an over 25% increase in serum prostate-specific antigen (PSA) within two consecutive measurements separated by at least one week, with a 2.0 ng/mL minimum increase over the starting value, and PSA doubling time is also incorporated to predict the aggressiveness of progression; and or the progression of visceral metastases, at least a 2 cm length of lymph nodes on computed tomography or magnetic resonance imaging is required. Finally, the castrate environment is defined as a serum testosterone concentration below 50 ng/dL or 1.7 nmol/dL [3].

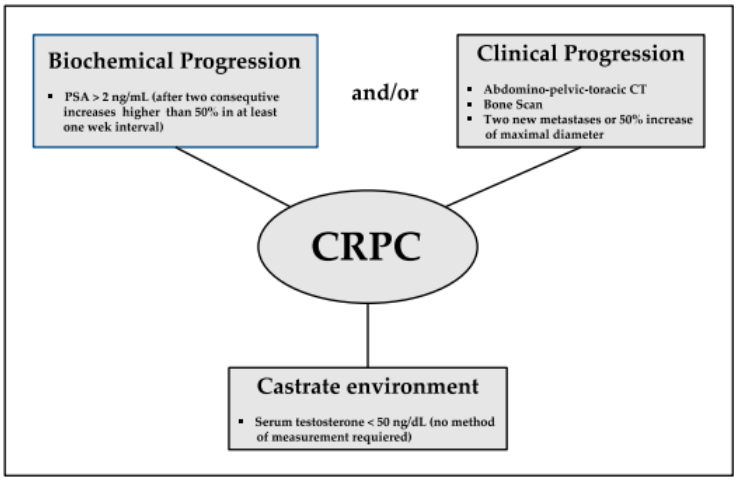

Figure 1: Current definition of Castrate Resistant Prostate Cancer

Source: Morote et al. "Definition of Castrate Resistant Prostate Cancer: New Insights" *Biomedicines* 10, no. 3: 689.

Abiraterone-Zytiga, Yonsa:

Androgen signaling axis continues to play a main role in CRPC. Thus, Antiandrogenic drugs have been discovered for more optimal management of CRPC. First-generation antiandrogens established androgen receptor blockade as a therapeutic strategy, but they fail to completely block androgen receptor activity. Efficacy and potency have been improved by the development of second-generation antiandrogen therapies, which remain the standard of care for patients with CRPC. Four second-generation anti-androgens are currently approved by the Food and Drug Administration (FDA); abiraterone acetate, enzalutamide, and recently approved apalutamide and darolutamide[4]. In this review paper we will discuss efficacy and potency of Abiraterone acetate (AA) and find out if there is correlation of its drug metabolism with disease progression.

With multiple high-level evidences of efficacy and safety, AA is considered a breakthrough in the treatment of CRPC. AA is a selective irreversible inhibitor of CYP 17. It is orally administered and is converted to its active metabolite abiraterone by the liver. Increased adrenocorticotrophic hormone drive, however, results in increased risks of hypertension and hypokalemia. In Phase III trials, AA with prednisone was shown to improve survivals in men with metastatic CRPC. The overall tolerability and safety profiles were acceptable.

Current clinical challenge, however, is to better delineate the mechanisms of the disease progression and their correlation with drug metabolism for developments of resistance to targeted therapies.

Drug metabolism:

The adrenal production of androgen precursor steroids, such as dehydroepiandrosterone (DHEA) and DHEA-sulfate (DHEA-S), permits intratumoral production of testosterone and 5α-dihydrotestosterone

(DHT), activation of androgen receptor (AR) and AR-dependent gene expression. This mechanism ultimately leads to development of treatment resistance in CRPC. AA is a potent inhibitor of 17α-hydroxylase/17,20-lyase (CYP17A1), which is a key enzyme required for DHEA and DHEA-S production. Synthesis of DHT, the most potent androgen, from DHEA necessitates a series of enzymes, including 3β-hydroxysteroid dehydrogenase (3βHSD), steroid-5α-reductase (SRD5A), and 17β-hydroxysteroid dehydrogenase (17βHSD) isoenzymes. This process enables the conversion of ADT-responsive prostate cancer into CRPC. To date there are very little data on the appropriate sequence of AA utilization, which might thereby maximize the potential efficacy and duration of response to treatment with these agents. Recently published article Li Z et al demonstrates that Δ^4, 3-keto-abiraterone (D4A) is a metabolite of AA that is formed in patients with prostate cancer and has CYP17A1 inhibition activity that is comparable to AA. They also found that D4A inhibits 3βHSD (a key enzyme involved in CRPC progression) more potently than AA and at higher concentrations it demonstrates significant SRD5A inhibitory effects as well. Moreover, although Abi has been shown to have AR antagonistic activity [5], we observed more potent AR inhibition activity with D4A that is comparable to Enzalutamide in our experiments [6]. As a result, by targeting multiple steps of the AR signaling pathway, D4A showed a significant increase in progression free survival compared to Abi and Enzalutamide in our xenograft models, suggesting that it might play an important role in the clinical activity of Abi in CRPC patients [7].

AA is converted to D4A by 3βHSD. Increased 3βHSD enzymatic function, with the *HSD3B1(1245C)* genetic variant encoding a missense in 3βHSD1 as one known mechanism, also increases intratumoral flux to DHT that may result in the development of treatment resistance. Therefore, D4A conversion ratio could serve as an indicator of 3βHSD activity and ultimately may predict resistance to hormonal therapy in prostate cancer. On the other hand, higher 3βHSD activity would translate into a higher D4A concentration, which is a more potent metabolite than AA as described above. A higher conversion ratio of AA to D4A might mimic conditions of treatment with those of AR antagonists. In other words, 3βHSD activity level in a patient might be helpful in predicting the potential response to AA. Thus, patient with higher concentration of D4A with AA treatment might be less likely to benefit from subsequent Antiandrogenic treatment. Conversely, AA conversion to D4A may increase the potential efficacy of the treatment with AA. In addition, because 3βHSD is required for mineralocorticoid synthesis, 3βHSD inhibition by D4A might reduce mineralocorticoid production that could translate into a better side effect profile (less hypertension and hypokalemia) and potentially lower dose of prednisone requirement in patients with higher D4A levels. These are recently established questions regarding AA metabolism with AA efficacy correlation that are yet to be answered in clinical studies. Finally, it is possible that drug metabolites of AA are not limited to D4A, and that other metabolites with clinically relevant biochemical activity contribute to response and resistance to treatment with AA [8].

Future prospective:

The main goal of this paper was to review available data on discovered Abiraterone agent metabolic

properties and their correlation to produced drug resistance. As we know clinically different patients with castration resistant prostate cancer reply differently for AA therapy, and interestingly poor reply to AA results in poor reply to other Antiandrogenic. Understanding the mechanism of AA utilization in molecular basis and mechanisms of drug resistance will maximize the potential efficacy and duration of response with treatment in CRPC. More detailed research on correlation between drug metabolism and cancer resistance and cancer progression can give us new insights for optimized approach in management of prostate cancer patients.

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