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Review

Combined blockade of testicular and locally made androgens in prostate cancer: A highly significant medical progress based upon intracrinology

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ABSTRACT

Recently two drugs, namely the antiandrogen MDV-3100 and the inhibitor of 17α-hydroxylase abiraterone have been accepted by the FDA for the treatment of castration-resistant prostate cancer (CRPC) with or without previous chemotherapy, with a prolongation of overall survival of 2.2–4.8 months. While medical (GnRH agonist) or surgical castration reduces the serum levels of testosterone by about 97%, an important concentration of testosterone and dihydrotestosterone remains in the prostate and activates the androgen receptor (AR), thus offering an explanation for the positive data obtained in CRPC. In fact, explanation of the response observed with MDV-3100 or enzalutamide in CRPC is essentially a blockade of the action or formation of intraprostatic androgens. In addition to the inhibition of the action or formation of androgens made locally by the mechanisms of intracrinology, increased AR levels and AR mutations can be involved, especially in very advanced disease. Future developments look at more efficient inhibitors of the action or formation of intraprostatic androgens and starting treatment earlier when blockade of androgens can exert long-term control and even cure prostate cancer treated at a stage before the appearance of metastases.

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Contents

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1. Introduction

Remarkable recent success has been achieved in the therapy of metastatic prostate cancer with two new androgen-blocking agents having been accepted by the FDA with a prolongation of overall survival of 2.2–4.8 months. These pertain to abiraterone (3.9 months) [1,2] and enzalutamide (4.8 months [3] or 2.2 months [4]). While prolongation of life is of benefit, metastatic prostatic cancer remains non-curable.

Starting with the observations of [5] which demonstrated the role of testicular androgens, the standard first line therapy of metastatic prostate cancer has been surgical or medical castration [6] which reduces the circulating testosterone levels by more than 95% (Fig. 1). In such advanced disease, castration alone or an antiandrogen alone provides a temporary positive response and progression to castration-resistant prostate cancer (CRPC) is the rule [7,8]. It should be mentioned that castration alone in metastatic prostate cancer has never shown a statistically significant prolongation of life. In fact, with the improved understanding of androgen formation and metabolism in men, castration alone is not anymore a science-based choice since it does not take into account the fact that in men, in addition to the testicular Leydig cells, another source of intraprostatic androgens is present and must be controlled. Most importantly, the role of this non-testicular source of androgens cannot be estimated by the concentration of blood testosterone which simply reflects a variable and very small leakage of intracellular androgens into the extracellular space [7,9] (Fig. 1).

The recent success obtained with abiraterone, an inhibitor of DHEA biosynthesis (Zytiga®, Johnson & Johnson) [1] and MDV-3100, a pure inhibitor of the androgen receptor (AR) (enzalutamide, X-tandi, Medivation – Astellas) [3,4] in CRPC patients has clearly revitalized and very convincingly illustrated the major importance of the previously described extragonadal androgen biosynthesis [7–14]. Despite such remarkable and well appreciated progress permitting the prolongation of life mentioned above (Tables 1 and 2), prostate cancer remains a major medical problem and is still the second cause of cancer deaths in men with 233,000 new cases to be diagnosed and 29,480 deaths estimated to occur in the United States alone in 2014 [15].

Although improvements in surgery and radiotherapy have occurred, National Cancer Institute data from 2.1 million patients with cancer in the USA between 1975 and 1995 have led to the conclusion that "cancer-fighting drugs improved survival rates, especially for cancer of the prostate, where drug innovations have been the greatest" [16]. In fact, for prostate cancer, the most important drugs have been gonadotropin-releasing hormone (GnRH) agonists [6] and pure anti androgens [17], thus permitting the co-administration of a pure antiandrogen with medical or surgical castration in order to achieve combined androgen blockade (CAB) [7,9].

Following the scientific and medical advances made starting with medical castration in the 1980s [6,18], soon followed by combined androgen blockade [7,9], it appears timely to look at the recent developments in the whole context of hormone therapy of prostate cancer, the most efficacious and well tolerated treatment of this very common disease (Fig. 2). Prostate cancer is more sensitive to hormone therapy than any other cancer [19]. It is thus appropriate that every effort should be made to take advantage of this unique characteristic and develop and use drugs that have the optimal efficacy at all stages of the disease.

2. How the extratesticular source of androgens (intracrinology) was discovered and resulting combined androgen blockade therapy applied

2.1. Medical castration with GnRH agonists

As mentioned above, it was discovered in 1980 that complete medical castration is achieved in men by chronic administration of GnRH agonists [6,18]. This discovery was particularly important for patients with localized prostate cancer who need long term and well-tolerated therapy. In fact, because GnRH agonists are psychologically and medically much more acceptable than orchidectomy or high doses of estrogens, these agents were rapidly accepted worldwide to achieve medical castration [6,20,21].

Although GnRH agonists rapidly became the standard treatment worldwide to eliminate testicular androgens, early biochemical studies using human prostatic tissue have shown that androgens are also synthesized in the prostate from dehydroepiandrosterone (DHEA), an inactive precursor of sex steroids produced by the adrenal glands (Fig. 3) [7,22–27]. The contribution of extratesticular androgens to total androgens is illustrated by the concentration of serum androgen metabolites remaining in the blood after castration and by the parallel levels of intraprostatic DHT (the most potent naturally occurring androgen) remaining in the prostate after castration [7,22–25] (Fig. 1). In fact, serum levels of testosterone (testo) are reduced by 97% following castration in men aged between 69 and 80 years (Fig. 1A) [23]. However, the sum of concentrations of androgen metabolites (the total androgen pool) – the most accurate method of measuring total androgenic activity in the circulation [28] – is reduced by only 59% (Fig. 1B).

The above-indicated data indicates that 41% of androgens are still present in the prostate and free to stimulate prostate cancer after elimination of testicular androgens. The data is in close agreement with measurements of intraprostatic DHT concentrations, which show, as mentioned above, that, on average, DHT concentration in the prostate after castration is 39% that observed in intact men (Fig. 1C) [7,22,29,30], while another study has demonstrated that intraprostatic DHT levels remained at 50% of intact values after castration [31].

Proof of an extratesticular source of androgens in the prostate was also provided by the addition of dutasteride and ketoconazole to combined androgen blockade (CAB) for 3 months prior to prostatectomy with a lowering of prostatic DHT from 0.92 ng/g in the CAB arm to 0.03 ng/g in the steroid inhibitor-treated arm [32]. Similarly, treatment of castrated patients with the potent CYP17A inhibitor abiraterone in patients already receiving a GnRH agonist decreased intraprostatic DHT levels from 1.3 ng/g to 0.18 ng/g and also decreased intraprostatic (dehydroepiandrosterone DHEA) [33].

2.2. Extratesticular source(s) of androgens (intracrinology)

It is very important to realize that castration, contrary to the misleading impression given by the ≥95% decrease in serum testosterone, is leaving an important concentration of intraprostatic androgens as clinically demonstrated as early as 1982 [9] (Fig. 2). In that study, CRPC patients (as recently called) showed a significant level of response upon addition of flutamide to castration. One first example of such a CRPC patient was a castrated man with paraplegia due to disseminated bone metastases who received daily flutamide for about two weeks and then, could walk out of the hospital by himself. Such an observation convinced the members of our group of the clinical importance of the extratesticular androgens in prostate cancer.

Adrenals that secrete large amounts of DHEA that is the source of androgens and/or estrogens in peripheral tissues is unique to the