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Review Article

Revisiting nomenclature for the description of prostate cancer androgen-responsiveness

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Abstract: Ever since the Noble prize-winning findings of Huggins and Hodges, the androgen receptor (AR) has been the main target for treatment of advanced prostate cancer (CaP). Today, second- and even third-line androgen deprivation strategies, which have been designed rationally to interfere with the AR signaling that re-emerges under conditions of androgen deprivation and is at least in part responsible for disease recurrence, are effective in impeding progression of advanced CaP. The therapeutic success of these novel agents in CaP that has failed initial androgen deprivation therapy (ADT) and subsequent chemotherapy is prompting studies to explore their use earlier in the course of CaP progression. Repositioning of these drugs, along with alterations in the timing, sequencing and/or combination of traditional or novel ADTs, either alone or in combination with radiation or chemo- or immunotherapies are expected to broaden significantly the scope of treatment options for CaP. Despite the rapidly changing and continuously innovating landscape of CaP therapies that target AR activity, the terminology that is used to describe CaP androgen status has not evolved. Currently available nomenclature falls short in capturing the sustained androgen-responsiveness of most CaPs after ADT, does not distinguish readily between CaP's responsiveness to androgens and other steroid hormones, and does not specify the treatment condition(s) under which CaP recurs. A novel vocabulary is introduced to solve these limitations and to facilitate optimal communication among physicians, scientists and CaP patients.

Keywords: Androgen receptor, androgen deprivation therapy, prostate cancer, hormones

Recently, survival benefits have been reported using the androgen biosynthesis inhibitor abiraterone acetate, or the second generation antiandrogen, enzalutamide, in patients who suffer from metastatic prostate cancer (CaP) that has failed first-line androgen deprivation therapy (ADT) [1-3]. The clinical benefits that are derived from these novel CaP drugs underscore the relevance of the androgen receptor (AR) signaling axis in advanced CaP, and endorse the validity of AR as a therapeutic target throughout the clinical progression of CaP.

The role for androgens and their cognate receptor in the development and progression of CaP has long been recognized and has served as the rationale to develop ADT, the first systemic CaP treatment, which has been the standard of care for patients with non-organ confined CaP for 7 decades [4-6]. Recurrence of disease during first-line ADT, which interferes with the interaction between gonadal androgens and AR, was interpreted originally to indicate that AR had lost its significance as a target for therapy in this stage of the disease. Ketoconazole provided secondary ADT, which was directed at adrenal androgens [7], but fell out of favor due to side effects from lack of specificity. The appreciation that a reawakening of AR signaling axis underlies, at least in part, CaP recurrence in the presence of castrate levels of serum androgens, dates back less than 10 years and led to the recent development and clinical success of second-line ADT [8-12].

None-the-less, the terminology that resulted from the initial misconception still lingers, and has left the field with a large set of descriptors for CaP that recurs clinically during first-line ADT that does not capture appropriately its androgen status and impedes efficient communication. Common shortcomings in the vocabulary

Table 1. Descriptors for prostate cancer that recurs during first-line androgen deprivation therapy

Commonly used	Nomenclature less than appropriate because
Androgen-independent	-cancer continues to rely on androgens for growth
Castration-resistant	-cancer almost always underwent remission after primary castration and often does not resist secondary or even tertiary castration approaches
Hormone-resistant	-cancer is not resistant to further manipulation of its endocrine and intracrine milieu
	-descriptor does not distinguish between androgens and other hormones
Androgen depletion-independent	-cancer remains responsive to further androgen depletion approaches
Hormone-relapsed	-descriptor does not distinguish between the cancer's responsiveness to androgens and other hormones
	-descriptor does not specify if relapse occurred under hormone supplementation or hormone depletion
Recurrent	-descriptor does not specify the conditions under which cancer recurred
Currently preferred	Most appropriate nomenclature to date because
castration-recurrent	-descriptor labels accurately cancer as disease that undergoes a remission and then recurs despite castrate serum levels of androgens

used to describe CaP that reemerges during ADT include the failure to acknowledge the sustained role for AR or androgens in CaP cell growth, the inability to distinguish between CaP responsiveness to androgens and other (steroid) hormones, and the lack of appreciation for CaP sensitivity to further therapeutic manipulation of its intracrine androgenic milieu (**Table 1**). Today, castration-recurrent CaP (CR-CaP) is the preferred and most accurate designation as it summarizes best the characteristics of advanced CaP treated by ADT: CaP regressed upon initiating ADT but then grows despite castrate levels of circulating androgens to produce clinical recurrence.

While superior and preferable to the other descriptors listed in **Table 1**, the term CR-CaP has limitations, which are likely to become more pronounced in the rapidly evolving and expanding landscape of treatment regimens for advanced CaP. Most obviously, CR-CaP does not allow for discrimination between CaP that fails first-line ADT and CaP that recurs during second-line androgen deprivation. AR-dependent mechanisms similar to those that underlie reemergence of CaP during initial ADT also appear responsible for disease recurrence during abiraterone or enzalutamide treatment, and the resulting disease has been suggested to be sensitive to further manipulation of the AR signaling axis [13-15]. Thus, it will be necessary to develop a nomenclature that is able to distinguish between CaP that reappears during initial, secondary, and even tertiary ADT. Similarly, the use of the terminology CR-CaP does not specify if castration has been achieved through surgical or medical means. CR-CaP also does not consider the class of drugs given to induce medical castration, whether or not antiandrogens were administered to achieve "complete" androgen blockade, or if ADT was continuous or intermittent. These nuances are relevant as the side effects that are associated with these treatment options differ and can affect significantly a patient's quality of life [16]. The selection pressure of ADT may induce more aggressive behavior of CaP cells that is likely related, at least in part, by a shift in the transcriptional program under control of AR [17-19]. The manner in which androgen deprivation is accomplished may affect differentially CaP cell biology. In addition, a more effective terminology to describe CaP androgen-responsiveness should provide information on the timing of ADT in the course of disease progression. For example, ADT prior to radical prostatectomy (RP) is no longer recommended but was applied routinely during the 1990s. Today, (pre) treatment of men who go on to develop CaP with 5α-reductase inhibitors, a means to interfere with conversion of testosterone to its more bioactive ligand, dihydrotestosterone, which is gaining momentum as a chemoprevention approach to CaP [20, 21], could be deemed a form of pre-RP ADT. The effects of pre-operative ADT on CaP behavior or the activity of the AR signaling axis remain largely unknown.

Table 2. Novel method of uniform prostate cancer nomenclature

Principle
Nomenclature provides a succinct and individualized summary of CaP androgen-responsiveness, treatment history and disease progression.
Examples
Case #1
A 68 year old man presents with Gleason grade 5+5=10 CaP and serum PSA 1,000 ng/ml. He receives continuous ADT using leuprolide acetate and bicalutamide. Superscan and serum PSA values demonstrate no response to treatment.
Summary: This case represents a truly castration-resistant CaP. Castration-resistant CaP is rare; only 2 to 3 % of newly diagnosed CaP fit this description.
Recommended nomenclature: LHRH-resistant and bicalutamide-resistant CaP
Case #2
A 68 year old man presents with metastatic CaP and serum PSA value 100 ng/ml 8 years after RP for Gleason grade 3+3=6 organ-confined disease. An induction course of leuprolide acetate causes his serum PSA levels to become undetectable and his bone scan to normalize. Five years later, his serum PSA level starts to rise. He is placed on intermittent ADT using leuprolide acetate for PSA parameters >20 and <1. He responds to each of several cycles, however the responses diminish until his CaP no longer responds to ADT.
Summary: This case represents an exquisitely androgen-responsive CaP that responds well to several cycles of ADT until the CaP becomes unresponsive to even continuous ADT.
Recommended nomenclature: RP-recurrent, LHRH agonist-recurrent, intermittent LHRH agonist-recurrent CaP
Case #3
A 68 year old man presents with metastatic CaP and serum PSA 100 ng/ml 2 years after RP for Gleason grade 4+3=7 pT3bN0M0 disease. He is administered continuous ADT in the form of leuprolide acetate. PSA declines but, six months later, serum PSA levels start to rise. He is administered antiandrogens using bicalutamide. PSA declines but, six months later, serum PSA levels start to rise. After discontinuation of bicalutamide, he experiences antiandrogen withdrawal syndrome, until his PSA levels rise again 4 months later. He is administered docetaxel until serum PSA levels rise 6 months later. He is given abiraterone acetate; PSA declines but, 6 months later serum PSA levels start to rise. He is administered enzalutamide. Five months after an initial response, PSA levels start to rise. He is administered Sipuleucil-T; 6 months after the start of treatment, PSA levels start to rise again.
Summary: This case represents a CaP that initially responds to and ultimately fails multiple ADT and other therapeutic approaches.
Recommended nomenclature: RP-recurrent, LHRH agonist-recurrent, bicalutamide-recurrent, docetaxel-recurrent, abiraterone acetate-recurrent, enzalutamide-recurrent, Sipuleucil-T-recurrent CaP

In the current post-RP setting, the therapeutic success of second-line ADT and the increased affinity of novel antiandrogens, such as enzalutamide, make it likely that these intervention methods, which were developed initially to offer novel treatment options for late-stage CaP, will be administered earlier in disease progression. Phase I and II trials have indicated already clinical benefits when these compounds are administered to chemotherapy-naïve patients [22-25].

A timelier and more effective blockade of the AR signaling axis is believed to benefit patients since it could delay disease progression [26]; whether the associated selective pressure results in a more aggressive CaP phenotype has not been determined. Ideally, terminology also should take in consideration whether ADT is given neoadjuvant to, adjuvant to or concomitant with other therapeutic approaches, such as radiation or immunotherapy. Combination treatments give rise to more severe side effects and alter disease behavior, which may complicate follow-up and biomarker-dependent assessment of efficacy of therapy [27].

A novel nomenclature is proposed to resolve the limitations that are associated with current descriptors for the androgen status of CaP (**Table 2**). Improvements to the terminology include that it summarizes the timing, sequence and combination of the treatments that have been applied and specifies the drugs that have been administered in the course of disease progression. Information provided by this

revised terminology better reflects the androgen-responsiveness of the tumor, allows for an initial assessment of the treatment course that has been administered, facilitates recognition of side effects from the various interventions since they are clearly identified and enables consideration of further therapeutic interventions, and their implications for future disease management, disease monitoring and patient stratification. In the latter respect, the application of the proposed terminology will facilitate the planning and interpretation of results from expression profiling and NextGen analyses of advanced CaP.

The revision of the current nomenclature also includes a term to label more appropriately CaP before treatment. Commonly used descriptors for CaP that has not undergone ADT reflect the well-known variation in response to ADT, and consist of the terms androgen-dependent, androgen-independent, and androgen-sensitive. Androgen-dependency of CaP cells implies that androgen deprivation leads to apoptosis and remission of CaP. On the other hand, androgen-independent CaP is not expected to display a measurable clinical response to ADT; this applies only to rare cases. Most CaPs exhibit a response to ADT that falls between these extremes, which underlies the labeling of ADT-naïve CaP cells as androgen-sensitive. The latter description suggests that CaP cells become quiescent until androgen supply is restored. To date, it is not feasible to assess accurately the percentage of CaP cells that are proliferating or undergoing apoptosis using biopsy material, nor can response to ADT be evaluated using available imaging modalities. Therefore, the term androgen-stimulated (AS), which circumvents the assumption of androgen-dependence or androgen-sensitivity for a given tumor, is recommended to describe CaP that has not been subjected to ADT.

This novel, uniform method of CaP nomenclature offers several benefits: it provides a succinct and individualized summary of CaP androgen-responsiveness, treatment history and disease progression, it specifies whether androgen deprivation is directed against gonadal, adrenal and/or cholesterol metabolism-derived androgen biosynthesis, it is flexible and adopted easily to incorporate future therapeutic intervention methods, and it is applicable to commonly used CaP model systems (cell line, cell line xenograft, primary explant xenograft). Most importantly, this method will improve considerably the quality of communication among physicians, scientists and CaP patients.

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