The changing landscape of advanced and castration resistant prostate cancer: latest science and revised definitions

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Introduction: *One fifth of men with newly diagnosed prostate cancer present with locally advanced or metastatic disease. Androgen deprivation therapy (ADT) is the standard systemic therapy in these patients. Despite initial response, essentially all patients will develop castration resistant prostate cancer (CRPC). In this review, we will discuss the revised definitions of CRPC and the latest understanding of the biology of the androgen/androgen receptor axis in the development of advanced prostate cancer.*

Materials and methods: *A systematic literature review was conducted via electronic database articles based on title, abstract, study format, and content. The majority of selected articles were published between 1992 and 2013. Older studies were included selectively if historically relevant.*

Results: *Prostate cancer becomes castration resistant through numerous pathways, including androgen and androgen receptor (AR) dependent mechanisms as well as ligand and AR independent pathways. Therefore the terms androgen-insensitive and hormone-refractory should be avoided and replaced by the term castration resistant. Recent advances in understanding molecular mechanisms of castration resistance have led to development of novel CRPC therapeutics.*

Conclusions: *CRPC remains an incurable disease. Further understanding of the pathways involved in castration resistance will set the basis for development of therapies to increase survival in these patients.*

Key Words: castration resistant, hormone refractory, prostate cancer, androgen receptor, review

Introduction

Despite early-detection efforts prostate cancer remains the second-leading cause of cancer-related mortality in men in Western societies.[1] One fifth of men with newly diagnosed prostate cancer present with locally advanced or metastatic disease.[2] Androgen deprivation therapy (ADT) is the standard systemic therapy in patients with locally advanced prostate cancer, biochemically recurrent disease after failed curative treatment and metastatic prostate cancer. After initial response to ADT, the vast majority of these patients will go on to castration resistant disease within a median of 2 to 3 years.[3] ADT relies on the dependence of prostate cancer cells on androgen-receptor (AR) signaling.[4] Castration resistant prostate cancer (CRPC) represents a pressing therapeutic challenge. Currently it is believed that AR-mediated pathways remain active in CRPC. Mechanisms of castration resistance have been studied extensively in the last decade and have led to development of new therapeutic options including abiraterone acetate, an androgen biosynthesis inhibitor which blocks cytochrome P450-c17 (CYP17), and enzalutamide, an AR signaling inhibitor which prevents androgen binding, nuclear translocation and chromatin binding.[5-7]

The aim of this review is to summarize the revised definitions of CRPC and the latest understanding of the biology of the androgen/androgen receptor axis in the development of CRPC.

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Materials and methods

A systematic literature review was conducted via electronic database searches of PubMed/Medline. Searches were conducted with the following combinations and iteration of the following terms: castration resistant prostate cancer, castration resistant, CRPC, prostate cancer, androgen resistance, hormone-refractory, hormone-independent, androgen receptor, androgen receptor axis. Articles were selected based on title, abstract, study format, and content by a consensus of the authors. The majority of selected articles were published between 1992 and 2013. Older studies were included selectively if historically relevant or in case of scanty data in more recent publications.

Results

Changes in the spectrum of advanced prostate cancer clinical presentation

The rate of patients with locally advanced (clinical T3/4NX/+M0) and metastatic prostate cancer at time of presentation has declined since the introduction of prostate-specific antigen (PSA). Nevertheless, these men contribute disproportionately to prostate cancer mortality and morbidity from this disease. PSA screening has also led to a change in clinical presentation of these patients. While patients presented with local symptoms due to locally advanced disease or cachexia, fatigue and bone pain in the pre-PSA era, PSA screening led to diagnosis of locally advanced prostate cancer in asymptomatic patients. It has been recognized that in patients with no evidence of nodal or metastatic disease, reliance on the T stage alone to define locally advanced disease and risk groups within it is not sufficient.[8] Therefore inclusion of pretherapy clinical and pathologic parameters other than clinical T stage such as PSA and Gleason score have led to a broader definition of locally advanced disease and are used to identify men at high risk for prostate cancer progression.[8,9]

Similarly as to patients at time of presentation, PSA has launched a new "clinical state" for CRPC as well, namely patients with or without clinical metastases, who have an increasing level of PSA despite ADT, but no obvious signs of progression based on clinical criteria or available imaging modalities.[10] Metastatic CRPC has a poor prognosis with a mean survival of 16-18 months.[11]

An emerging clinical phenomenon is the finding that up to 25% of men with late stage prostate cancer have a neuroendocrine phenotype.[12] Poorly differentiated neuroendocrine prostate cancer (small cell carcinoma of the prostate) is an aggressive disease and is frequently accompanied by presence of visceral metastases. Neuroendocrine tumors lack AR, do not secrete PSA and show poor response to androgen ablation. While neuroendocrine prostate cancer as a primary diagnosis is rare, neuroendocrine differentiation of prostate cancer increases with disease progression and in response to ADT,[13] which is likely due to selective treatment pressures driving the tumor to become less reliant on signaling through AR. This is therapeutically problematic and mandates finding new mechanisms for tumor growth inhibition.

New definitions of castration resistant and metastatic CRPC

With the demonstration of prostate cancer shrinkage via hormone therapy in 1941, the foundations were laid for a new disease, namely castration resistant prostate cancer.[14] New insights into mechanisms of prostate cancer resistance to ADT over the last two decades have led to revised terminologies of this disease.

Despite initial response to hormone therapy, the majority of patients with advanced prostate cancer will progress within a median of 2 to 3 years from the start of ADT.[15] Prostate cancer cells survive and resume growth despite ADT via adaptation to androgen-depleted conditions and alternative survival and growth pathways.[16,17]

This state of disease was widely referred to as hormone-refractory prostate cancer. The term suggests that further hormonal treatment of the prostate cancer will not be useful.

In 1982, Fowler and Whitmore observed that administration of testosterone led to unfavorable responses especially in those patients who were in symptomatic relapse following endocrine therapy.[18] These results indicated that although the prostate cancer was progressing despite ADT, it was still responding to androgen action and therefore not independent of or refractory to androgens.

Different additional hormonal therapy strategies including maximum androgen blockade, antiandrogen withdrawal, variation of specifc antiandrogens (e.g. bicalutamide, flutamide, nilutamide), estrogen compounds (diethylsilbestrol), adrenal suppressants (ketoconazole) have proven helpful.

Recognizing that the term hormone-refractory was used heterogeneously in a broad spectrum of prostate cancer patients, in 1999 Scher et al proposed a refinement of the classification of patients with relapsing disease despite ADT.[19] The authors reviewed 19 trials of relapsed patients under ADT and found that only one included a definition for hormone-refractory disease based on at least two values of elevated PSA.[19]

Furthermore, in the evaluation of second line hormonal therapies, patients were included who had one to up to six different treatments before enrollment in the same study.[19] Scher et al presented a classification scheme based on hormone sensitivity including the following three categories: 1) Hormone-naive patients who show a decrease in tumor proliferation if androgens are withdrawn or antiandrogens are administered (physiologic levels of androgens in the blood). 2) Androgen-independent and hormone-sensitive patients with decrease in proliferation in response to other hormonal manipulations as mentioned above (castration levels of testosterone). 3) Hormone-independent (androgen-independent and hormone-insensitive) patients who are insensitive to hormonal manipulations (castration levels of testosterone).[19] Extent of prostate cancer has not been included in these definitions, while the later introduced clinical states model of prostate cancer did differ castration resistance based on rising PSA from different states of castration resistance based on clinical metastases.[20,21]

Extensive research in the past decade has uncovered several underlying mechanisms by which prostate tumor cells become resistant to hormone therapy (as discussed below) and led to new definitions for prostate cancer progression despite castration levels of testosterone.

Testosterone levels of < 20 ng/dL after surgical castration have been measured using chemiluminescent technology and suggested as a cut point to define castration.[22,23] Previous to clinical approval of this new technique for testosterone measurement, a castration cut off of 50 ng/dL was used.[23]

Given that the terms androgen-independent and hormone-refractory do not reflect the possibility that a patient may respond to alternative hormone therapies and despite its wide use, the term castration resistant prostate cancer has emerged and established as more accurate.

According to the Canadian Urological Association castration resistant prostate cancer is defined by disease progression despite androgen deprivation therapy and may present as either a continuous rise in serum PSA levels, the progression of pre-existing disease, and/or the appearance of new metastases.[24] Similarly, the American Urological Association guidelines define CRPC as a rising PSA level and/or radiographic evidence of prostate cancer progression despite medical or surgical castration.[25] The Prostate Cancer Clinical Trials Working Group 2 (PCWG2) defines PSA only failure as a rising PSA that is greater than 2 ng/mL higher than the nadir. The rise has to be at least 25% over nadir and confirmed by a second PSA at least 3 weeks later.[25,26]

Summary of the latest understanding of the biology of the androgen and androgen receptor axis in the development of CRPC

Prostate cancer growth and survival depend on androgens which regulate the ratio of cells proliferating to those dying.[15] Testosterone is the main circulating androgen, of which 90% is secreted by the testes. Only a small fraction (3%) of testosterone is unbound and functionally active, while most of it is bound to sex-hormone-binding globulin or albumin. After entry of free testosterone through the cell membrane into the cytoplasm via diffusion, it is converted to dihydrotestosterone (DHT) by the enzyme 5α-reductase.[15] The AR is a member of the nuclear receptor superfamily and acts as a ligand-inducible transcription factor. It consists of a polymorphic N-terminal domain, a central DNA-binding domain, a small hinge region, and a C-terminal ligand-binding domain.[27,28] The AR gene is located on the X chromosome and therefore is single-copy in males, which allows for the phenotypic manifestation of mutations without the influence of a wild-type codominant allele.[28] DHT has a five-fold higher affinity for the AR than testosterone.

The unliganded AR associates with a heat shock protein 90 (HSP90) chaperone complex in the cytoplasm and undergoes proteasome-mediated degradation in the absence of ligand.[29]

Androgen binding to AR results in dissociation of the AR-HSP-complex, homo-dimerization, and nuclear translocation. Subsequently the AR dimer binds to androgen response elements (ARE) in the promoter regions of target genes and recruits cofactors for regulation of the expression of androgen-regulated genes.[15,27,30,31] Other signal transduction pathways which involve TGF, IL-6, and IGF-I, can also enhance AR activity via phosphorylation of AR and/or AR coregulators.[31]

Approaches for ADT, as discussed in detail in the following articles of this supplement, are inhibition of luteinizing hormone (LH) or luteinizing hormone releasing hormone (LHRH), ablation of androgen sources, antiandrogens and inhibition of androgen synthesis. All of these therapeutic approaches have in common that they reduce AR activation through reducing levels of androgen or blocking AR binding. Therefore AR is believed to remain active in CRPC and to be critical in the development of CRPC.[29] Different androgen resistance mechanisms exist, which enable castration resistance. Molecular mechanisms which have been described to play an important role in CRPC are summarized in Table 1.[15,29,31,32] These include androgen and AR dependent

TABLE 1. **Possible molecular mechanisms of castration resistance (not exhaustive)**

Strategy/pathway	Mechanisms/references
Increased androgen sensitivity	• AR gene amplification[36,37] • AR stabilization[33] • Increased local androgen production (e.g. increased conversion of testosterone to DHT)[38] • Androgen transport[34,35]
Aberrant activation of the AR/promiscuity of AR (inappropriate AR activation by non-androgen steroids and androgen antagonists)	• AR mutations[41-44] • Alterations in AR coregulators[39,40]
Ligand independent AR activation/ altered AR transcriptional activity	• Activation of AR by growth factors (IGF-1, KGF, EGF)[48] • Receptor-tyrosine-kinase activated pathway (HER-2/ neu signaling cascade; Src kinase)[46,47,52,57] • AKT pathway[50,51] • E2C (UBE2C)[55] • Upregulation of AR (Rb/E2F/nuclear receptor axis; AR action on enhancer versus suppressor elements)[45,53] • AR splice variants (ligand-binding-domain deficient)[49,54-56] • lncRNA-dependent mechanisms of androgen-receptor-regulated gene activation programs[69]
AR independent pathways (activation of parallel survival pathways)	• Overexpression of oncogenes (BCL2 gene)[58-61]
Stem cells	• Androgen-independence before initiation of androgen deprivation therapy[70,71]
Intratumoral androgens	• Alternative intratumoral steroid biosynthesis pathway[73] • Fatty acids induced androgen synthesis[72]

AR = androgen receptor; DHT = dihydrotestosterone; IGF-1 = insulin-like-growth factor 1; KGF = keratinocyte growth factor; EGF = epidermal growth factor; BCL2 = B-cell lymphoma 2; UBE2C = ubiquitin-conjugating enzyme E2C gene; lncRNA = long non-coding RNA)

mechanisms[33-35] such as AR amplification[36,37] and local androgen production,[38] androgen independent and AR dependent mechanisms[39,40] such as AR mutations[41-44] and ligand independent AR activation,[45-57] as well as androgen and AR independent mechanisms such as alternative survival pathways.[58-61] Ligand-independent AR activation is postulated to eventuate from overexpression, mutation or, most commonly, truncation of the ligand-binding C-terminus of AR.[62-65] Loss of the C-terminus results in splice variants of AR that can be constitutively active. This likely occurs in about 25% of CRPC patients.[54,66] AR differs from other steroid receptors in that the transcriptional activity is mainly through the activation function region 1 in the N-terminal domain rather than in the ligand-binding domain.[67] Therefore treatment of splice variants requiring targeting of the N-terminus to date has lacking pharmacological success. Andersen and colleagues have reported that EPI-001, a marine sponge derivative, can inhibit transactivation of the N-terminal domain and block induction of androgen-regulated genes.[68] Recently it was reported that long non-coding RNAs regulate activation of both truncated and full-length AR, leading to ligand-independent activation of the AR transcriptional program.[69] Targeting the N-terminus is important and new approaches to inhibit AR are being developed.

Tumor-related factors proposed to contribute to castration resistance are stem cells[70,71] and intratumoral androgens,[72,73] Table 1. High levels of androgens in

CRPC samples and increased expression of androgen synthesis enzymes have been shown that tumor cells are involved in androgen synthesis and thus in AR reactivation.[29] Montgomery et al evaluated androgen levels and transcripts encoding steroidogenic enzymes in benign prostate tissue, untreated primary prostate cancer, metastasis from patients with castration resistant prostate cancer, and xenografts derived from castration resistant metastases.[74] They showed evidence that castration resistant metastatic prostate cancers may adapt to low systemic testosterone levels by maintaining intratumoral androgens through modulation of enzymes involved in intracrine steroidogenesis and androgen catabolism.[74] Locke and colleagues used the LNCaP xenograft model and showed that tumor androgens increase during CRPC progression in correlation to PSA up-regulation.[75] Furthermore, the authors demonstrated that all enzymes necessary for androgen synthesis are expressed in prostate cancer with some of them being up-regulated during CRPC progression.

The mechanisms driving the development of castration resistance likely vary among patients. Recently, persistent AR signaling activation has received much attention, leading to the identification of novel therapeutic targets.

Prostate cancer can acquire resistance to ADT through multiple mechanisms. Despite treatment of CRPC with new effective therapeutics such as enzalutamide and abiraterone acetate, all patients will eventually progress.[5,7] Resistance mechanisms evolve against most AR antagonists over time, and thus, it remains a valuable goal to develop other types of therapy targeting the AR or molecules that are specifically required for AR-regulated transcriptional programs. Combined and personalized treatment strategies and different treatment sequences are being evaluated to improve therapy of this disease.

Conclusions

Prostate cancer becomes castration resistant through numerous pathways, including androgen and AR dependent mechanisms as well as androgen/ligand and AR independent pathways. Therefore the terms androgen-insensitive or hormone-refractory should be avoided and replaced by the term castration resistant. Recent advances in understanding molecular mechanisms of castration resistance have led to development of novel CRPC therapeutics. Nevertheless, CRPC remains an incurable disease. Further understanding of the pathways involved in castration resistance will set the basis for development of therapies to increase survival in these patients.

Disclosure

Dr. Derya Tilki has no potential conflict of interest. Dr. Christopher P. Evans received honoraria from Janssen, Medivation, Astellas and has ownership interest in Oncogenex. □

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