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UPDATE ON CASTRATE RESISTANT PROSTATE CANCER

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ABSTRACT. Based on the increased understanding of the biochemical pathways that promote tumor survival a range of new treatments become available. Drug development based on biology-guided rationale coupled with intelligent trial design will find promising new treatment options for castrate resistant prostate cancer (CRPC). The androgen receptor plays the key role in prostate cancer even during castrate resistance, and therapies targeting it represent the future for treating CRPC. During progression to CRPC induced by persistent androgen deprivation, androgen receptor (AR) signaling is maintained through a variety of mechanism including increased expression of AR, amplification of the AR gene, and structural changes in AR caused by genetic mutations or mRNA splice variants. Clinical consideration has been added to the conventional staging criteria to describe the extent of the disease beyond the simple anatomic classification. For patients with metastatic CRPC who have previously received docetaxel chemotherapy Abiraterone acetate is a novel androgen biosynthesis inhibitor that has gained FDA approval. For men with asymptomatic or minimally symptomatic metastatic CRPC Sipuleucel-T is the first therapeutic vaccine to be FDA approved. Immunotherapy also has several potential benefits for patients with CRPC, including lack of toxicity and maintains of quality of life. It is an exciting time in the management of CRCP with new agents under development. Such evolution in treatment approach will necessitate an evolution of the urologist from being primary a surgeon to becoming more an applied molecular biologist.

KEYWORDS: Castrate resistant prostate cancer, androgen receptor, androgen receptor - independent and androgen receptor -dependent mechanism

After 3-5 years of androgen deprivation for develops and it is mediated through two main, treatment of prostatic cancer (PCa) androgen overlapping, mechanisms, which are AR-independent independence (now called castration resistance) and AR-dependent [1,2].

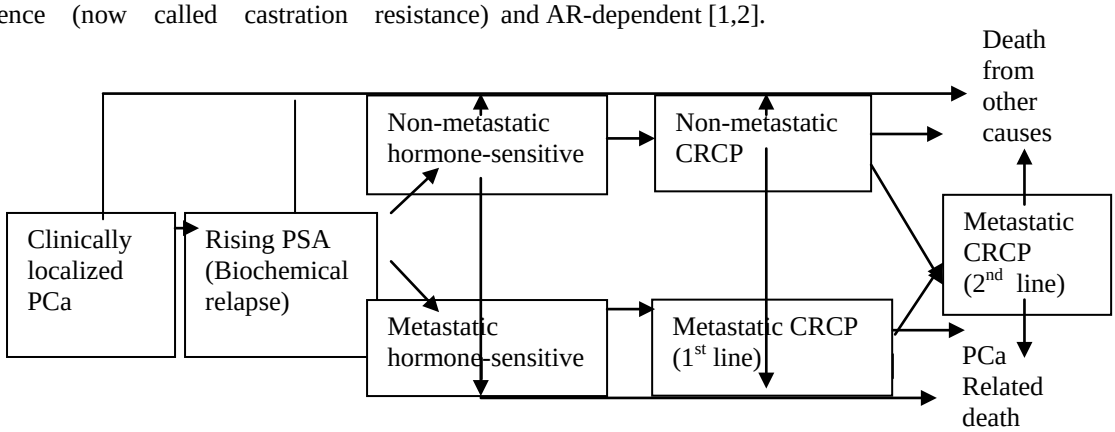

Fig.1.Prostate cancer clinical states: patients with castrate levels of testosterone develop progression with different clinical disease evaluation and responses to treatment [3]

The AUA guideline for CRCP presents a user friendly algorithm with six indexes to guide clinicians in patient management. The first index patient is asymptomatic and has no radiographic evidence of metastatic disease but has a rising PSA level. The second index patient is asymptomatic or minimally symptomatic and does have metastatic disease, but has received no prior chemotherapy. The third index patient is symptomatic, has metastatic disease and has good functional status and no prior chemotherapy. The forth index patient is symptomatic and has metastatic disease, but has

a poor functional status and have received no prior chemotherapy. The fifth index patient is symptomatic, has metastatic disease and has good functional status but disease has progressed after chemotherapy. The sixth index patient is symptomatic and has metastatic disease, poor functional status and disease progression after receiving chemotherapy. The new treatments and management options for CRCP address bone health and palliative care to improve patients Qol in the end stage of the disease [4].

Prostate cancer is extremely heterogeneous both from clinical characteristics and from its genetic and phenotypic combination. The evolution of PCa to the castrate resistance makes the disease deadly.

Using a co-clinical approach Lunardi et al. investigated the pathways involved in CRPC development. Mechanisms of ADT resistance were studied in murine models and human clinical data. The same genetic determinants were found to be associated with clinical responses to ADT and progression to CRPC in mouse models with specific genetic make-up of the tumor model and in human specimen analyses [5,6]. Lunardi et al. identified the expression patterns of Xaf1, Xiap and SRD5A1 as a predictive and actionable signature for CRPC. Combined inhibition of Xiap, SRD5A1 and AR pathways overcomes castration resistance. Androgen deprivation suppresses tumor growth in vivo when Xaf1 pathway was inhibited with embelin. In patients inhibition of these pathways (by embelin and dutasteride) improved patient response to ADT. The co-clinical approach facilitates the stratification of patients, and the development of tailored and innovative therapeutic treatments [5,6].

Prostate cancer cells on androgen deprivation therapy (ADT) develop castrate resistance by *persistent androgen receptor (AR) signaling*. The mechanisms involved are: amplification of the AR gene, increased expression of the AR protein, greater stability and nuclear localization of the AR protein, promiscuous activation of the AR protein by non-androgens (e.g. estrogens, progestin, and tyrosine kinases), ligand independent (constitutive) activation of AR protein and active ARmRNA splice variants[7,8,9].

Androgens levels within CRCP tumors remain high, despite circulating testosterone being below castrate level [7]. *Ectopic androgen synthesis* main mechanism is intratumoral androgen synthesis by increased conversion of extra-gonadal androgens to testosterone and androgen synthesis by adrenal glands [7,10]. CRCP maintained androgen–activated gene expression despite reduced levels of androgens with ADT[6,7]. In CRCP intraprostatic concentrations of T and DHT remain sufficient to stimulate AR. CRCP cells are able to convert androstenedione to T and *de novo* intratumoral synthesis through steroidogenic enzymes such as cytochrome P450 17 (CYP17)[9,10].

AR-mediated transcription functions with coactivators and corepressor signaling.
Modulation of AR co-regulators with overexpression of steroid receptor coactivators (e.g.p160, NCOA2), downregulation of steroid receptor corepressors (e.g. B-arrestin 2) and facilitation of AR-mediated transcription, facilitates or inhibits binding and activation of AR to androgen-response elements in promoter and enhancer of DNA regions[7,12,21].

AR-independent mechanisms may be associated with the deregulation of apoptosis through the deregulation of oncogenes. Loss of PTEN (phosphatase and tensin homologue deleted on chromosome 10) occurs in more than 50% of metastases and 20% of locally advanced lesions[20,21]. *Activation of compensatory AR-independent pathways* are: activation of the PI3K/Akt/mTOR pathway, activation of the Ras/Raf/MEK/ERK pathway, overexpression of anti-apoptoic proteins (e.g. Bcl-2, Bcl-XL, clusterin, survinin) and activation of other pathways (e.g. TGF-βR, Wnt/β-catenin, Src kinase, IL-6R)[7]. The mechanism through which bcl-2 induces its anti-apoptotic effect may be the regulation of microtubule integrity [11,14]. The tumor suppressor gene p53 is more frequently mutated in CRCP. The goal is to reproduce the phenotypic findings of prostate cancer and identify target causality, indicating the importance of the target alone or in combination with other mutations [14,15].

The past few years have brought increasing advances in the therapeutic management of CRCP with the approval of several agents, including vaccine therapy, second-line chemotherapy, and the bone-targeted pharmaceutical, and antiandrogen therapy. There are ongoing developments with other agents that have shown promising results[4,12].

Understanding of the biology involved of pathogenesis of prostate cancer provides the opportunity to develop new molecules that will improve the clinical outcome of the disease. Clinical trials are underway to target the bcl-2 pathway [15], as the MDM2 oncogene [16,17,19] and the PTEN (phosphatase and tensin homolog) suppressor gene. Evidence from preclinical models showed that inhibition of the target leads to tumor regression or quiescence.

In prostate cancer, the androgen receptor is one potential target although there are many others. Androgen receptor mutations may lead to a functional change in AR function [3,4,18]. At the same time, there is an intracellular increase in

androgens from in-situ conversion [13,16]. This increase may be secondary to an increase in the intracellular enzymes involved in intracellular androgen synthesis in some situations may provide the explanation for the responses associated with some therapeutic maneuvers (anti-androgen withdrawal syndrome, responses to secondary endocrine manipulations with compounds designed to bind to the receptor). Despite this, the role of the AR in the pathogenesis of progression to CRPC remains to be better elucidated.

In conclusion, existing data for the novel agents are promising, but ongoing trials are needed to optimize the sequencing and combining of existing and future therapies.

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