Chapter 59
How is castration-resistant prostate cancer now understood and treated?

Lara Rodriguez-Sanchez and Rafael Sanchez-Salas

According to the American Cancer Society, about one man in eight will be diagnosed with prostate cancer (PCa) during his lifetime. Conversely, "only" one man in 41 will die of the most common cancer among men, PCa. In other words, considering all patients diagnosed with PCa (most of them with local and potentially curable cancers), the probability of dying from this cancer 5 years after diagnosis is lower than 5%.

Indefinite hormonal suppression (through surgical castration by orchiectomy or chemical castration), whether continuous or intermittent, is the cornerstone of PCa treatment in two main scenarios: 1) when the disease is first diagnosed after it has already spread outside of the prostate to distant parts of the body or 2) when the disease progresses radiologically (appearance of metastasis) or biochemically (increase in PSA) after radical treatment with curative intent (Chapters 57, 58).

Up to 20% of PCa patients, metastatic or not, will progress to a more aggressive disease stage called castration-resistant PCa (CRPC). In contrast to the optimistic survival rates mentioned above, the median overall survival length of patients with CRPC is less than 5 years.

What does CRPC mean?

The National Cancer Institute describes CRPC as PCa that keeps growing even when the amount of testosterone in the body is reduced to very low levels. The name "CRPC" has been used synonymously with "androgen-independent PCa" ("AIPC") and "hormone-refractory PCa" ("HRPC"), but "CRPC" is the preferred and recommended term the PCa Working Group 2 (PCWG2) established.

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How are androgens related to PCa?

The prostate stromal microenvironment (normal cells, molecules, and blood vessels that surround and feed a tumor cell), as well as epithelial prostate cells are both influenced by androgen activity. Therefore, the development and progression of PCa is intimately associated with what are considered "male hormones," specifically testosterone and its active metabolite, dihydrotestosterone (DHT).

The hypothalamic-pituitary–gonadal axis is the basis of normal androgen production in men. (Chapter 2). As Fig. 1 shows, the hypothalamus secretes cortical stimulation hormone (CRH) and luteinizing-hormone-releasing hormone (LHRH) (also known as gonadotropin-releasing hormone (GnRH)). These hormones induce the release of the adrenocorticotropic hormone (ACTH) and the follicle-stimulating hormone (FSH) along with luteinizing hormone (LH) from the anterior pituitary gland. ACTH will induce the production of dehydroepiandrosterone (DHEA), a precursor hormone for testosterone. LH stimulates the production of testosterone by Leydig cells in the testes, whereas FSH stimulates testicular growth and enhances production of androgen-binding protein by Sertoli cells. Circulating testosterone, either on its own or when locally converted to DHT by 5α-reductases, is able to bind to cytosolic AR, that translocates into the nucleus and acts as a transcription factor, binding to specific DNA sequences, leading to the expression and/or suppression of a variety of genes that can promote, among other events, tumor cell proliferation.

Resistance to castration appears after suppressive treatments via surgical castration, or chemical castration using 1) molecules that compete with androgens at the receptor level, antiandrogens (e.g., bicalutamide, nilutamide, flutamide, or cyproterone acetate); 2) LHRH antagonists (e.g., degarelix); or 3) LHRH agonists (e.g., leuprolide, goserelin, and triptorelin), which lead to the down-regulation of the LHRH receptors consequently suppressing LH and FSH secretion and hence testosterone production.

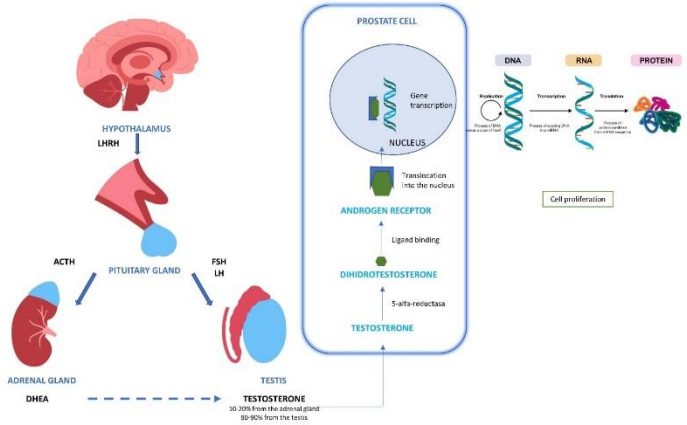

Figure 1. Hypothalamic-pituitary–gonadal axis and testosterone signaling pathway. LHRH; luteinizing-hormone-releasing hormone, ACTH; adreno-corticotropic hormone, FSH; follicle-stimulating hormone, LH; luteinizing hormone, DHEA; dehydroepiandrosterone.

How do PCa cells become androgen independent?

The way PCa becomes independent of androgen suppression is still a matter of debate, and some knowledge gaps remain; however, two main mechanisms have been described:

1. AR-dependent mechanism

Androgen signaling may persist despite androgen suppression due to mutation or amplification of AR genes and the consequent receptor overexpression, changes in expression of AR co-regulatory proteins, changes in expression of steroid-generating enzymes, or ligand-independent activation of AR via “outlaw” pathways.

2. AR-independent mechanism

Also known as “bypass” pathways. In this case, other non-androgenic ligands bind to their receptors, activating a signaling cascade independent of ARs leading to the transcription of genes involved in cell proliferation.

The understanding of the various ways tumor cells can continue growing regardless of the absence of androgens has been essential for the development of new therapeutic strategies to prolong the lives of patients who have reached one of the final stages of the disease.

What is the prognosis for patients with castration-resistant PCa?

Considering the natural history of PCa, this cancer begins as a localized disease. If the patient is diagnosed at this time, the therapeutic possibilities vary from active surveillance and focal treatment to radical treatment by either radical prostatectomy (with or without lymphadenectomy) or radiotherapy (with or without associated hormonal treatment). A percentage of these patients will experience a biochemical or radiological recurrence. As a first option, local salvage treatments with or without systemic treatment will be considered; however, such treatment will not always be possible, and an indefinite androgen blockage (intermittent or continuous) will be the basis of the treatment with the intention, at this point, not to cure the patient but to improve and prolong his life.

The median time from initiation of hormonal treatment to castration-resistant status is 2-3 years. The current specific criteria to define the status of castration resistance are: 1) serum testosterone levels less than 50 ng/dL or 0.7 nmol/L, and 2) 2 or 3 consecutive increases in PSA within two consecutive measurements separated by at least one week with a 2.0 ng/mL minimum increase over the starting value. In addition, documented disease progression based on findings from conventional imaging that includes bone scan and computed tomography scan using RECIST (Response Evaluation Criteria in Solid Tumors) are important diagnostic criteria.

CRPC can be categorized as either metastatic or nonmetastatic. Within approximately 1½ years, nonmetastatic CRPC will eventually spread. At this stage, currently the median overall survival expectancy is less than 3 years.

What are the treatment options for patients with CRPC?

We summarize therapeutic strategies for PCa in Fig. 2. In 1996, docetaxel was approved for the treatment of metastatic CRPC. Another taxane-based chemotherapeutic agent (drugs that interfere with microtubules blocking mitosis or cell division), cabazitaxel, was approved 14 years later for patients who have already received docetaxel treatment. In the same year, a type of therapeutic cancer vaccine, Sipuleucel-T, was launched as a new treatment option.

Due to advances in understanding the role of androgens in the various signaling pathways and cell proliferation, new therapeutic molecules have been developed in the last decade. These molecules are referred to as second-generation nonsteroidal AR inhibitors (ARis), androgen-receptor signaling inhibitors (ARSIs), and new AR-pathway-targeting agents (ARTA). We present the new AR antagonists and androgen synthesis inhibitors below:

Enzalutamide, apalutamide, and darolutamide

All three agents are novel anti-androgens with a greater affinity for the AR. These drugs have 3 complementary mechanisms of action:

1. competitive inhibition of androgen binding to the AR,
2. inhibition of nuclear translocation of the AR into the nucleus, and
3. inhibition of the AR binding to DNA, preventing the transcription of DNA into RNA.

Abiraterone

Its mechanism of action differs from those previously mentioned. Abiraterone blocks the enzyme CYP17, preventing the synthesis of testosterone in the testes, adrenal gland, and tumor cells.

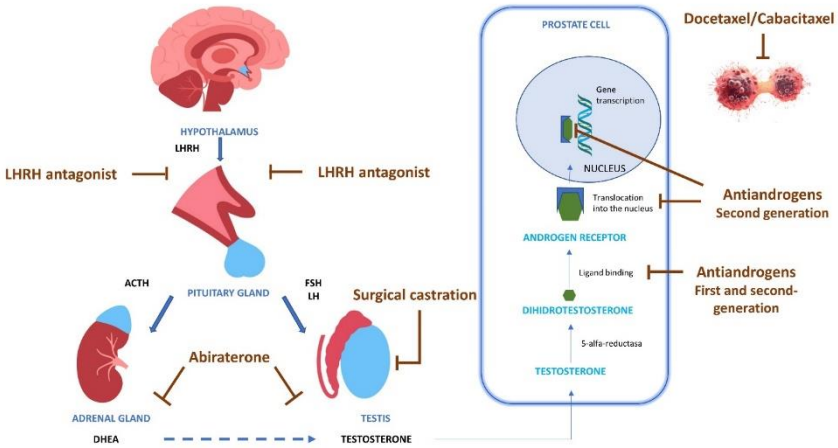

Figure 2. Therapeutic Strategies in PCa
LHRH; luteinizing-hormone-releasing hormone, ACTH; adrenocorticotropic hormone, FSH; follicle-stimulating hormone, LH; luteinizing hormone, DHEA; dehydroepiandrosterone.

Radium 223

A radiopharmaceutical that selectively targets bone metastases with alpha particles. This treatment is suitable for patients with symptomatic bone metastases but without known visceral disease or lymphadenopathy >3cm. It cannot be used in combination with chemotherapy or ARTA.

Poly(ADP-ribose) polymerase (PARP) inhibitors

PARP enzymes aim to identify and repair DNA damage. Therefore, PARP inhibitors will have a cytotoxic effect.

- Olaparib is indicated in the case of a deleterious germline or somatic homologous recombination repair (HRR) gene mutations.
- Rucaparib must be considered in the case of BRCA1 or BRCA2 mutations.

Pembrolizumab
This is a type of immunotherapy that blocks the programmed-cell-death protein (PD-1) located on the surface of T-cells. PD-1 induction is a kind of adaptive immune resistance because this protein's bond with its corresponding ligand (PD- L1) helps keep T-cells from killing other cells, including cancer cells. This compound has been approved for patients with microsatellite instability-high (MSI-H) or mismatch repair-deficient (dMMR) solid tumors.

Lutetium-177 (177Lu) prostate-specific membrane antigen (PSMA)-617
A radioligand therapy that delivers beta-particle radiation to PSMA-expressing cells (characteristics of PCa), inducing their death. In 2022, the US FDA approved the use of this drug for the treatment of patients with prostate-specific membrane antigen (PSMA)-positive mCRPC who have been treated with androgen receptor pathway inhibition and taxane-based chemotherapy

Sipuleucel-T
An immunological agent, may be administrated in patients with asymptomatic or minimally symptomatic nonvisceral metastases, a good performance status and a life expectancy superior to 6 months.

What are the treatment options based on the stage of the disease?

It is important to bear in mind that first-line androgen-deprivation therapy must be continued to maintain castrate serum levels of testosterone <50 ng/dl. The treatment chosen depends on the presence of metastasis, the PSA doubling time (the shorter the time, the greater the risk of metastasis), and the previous received treatment.

For non-metastatic Castration-Resistant PCa
if PSA doubling time >10 months, then continuous monitoring is the preferred option. If PSA doubling time <10 months, then use apalutamide, darolutamide, or enzalutamide

For non-metastatic Castration-Resistant PCa, four therapeutic approaches are possible

1. If no prior docetaxel and no prior novel hormone therapy was

used, then any of these are options: Abiraterone, Enzalutamide, Docetaxel, Radium 223, Sipuleucel-T;
2. If no prior docetaxel was administered, but prior novel hormone therapy was used, then any of these may be used: Docetaxel, Sipuleucel-T, Cabacitaxel/Carboplatin, Olaparib, Rucaparib, Pembrolizumab, Radium-223;
3. If prior docetaxel was used, but there was no prior novel hormone therapy then any of these may be used: Abiraterone, Enzalutamide, Cabazitaxel, Cabacitaxel/Carboplatin, Pembrolizumab, Radium 223, Mitoxantrone (palliative in symptomatic patients who do not tolerate other therapies);
4. If Prior docetaxel and prior novel hormone therapy were used then few options are available because chemotherapy and new AR-pathway-targeting agents, the mainstays of treatment for CRPC, have already been used. Nevertheless, in certain circumstances, patients may receive any treatment that has not been employed (e.g., Cabacitaxel/Carboplatin, pembrolizumab, radium 223, PARP inhibitors). In this scenario, Lutetium Lu-117-PSMA-617 may be considered under certain circumstances.

Although therapeutic approaches for the treatment of CRPC were stagnant for many years, we have witnessed a burst of novel approaches that have proven effective in prolonging the life of CRPC patients. Yet, none of these valuable approaches are providing a cure for this cancer. Refinement of these therapeutic approaches may further increase life expectancy, but we await the development of new, individual patient targeted approaches to provide avenues for curing CRPC.

Suggested reading

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