

Small-Molecule Drugs target Androgen Receptor (AR) signaling pathway for Prostatic Cancer Treatment

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Abstract. The fourth most common cancer worldwide is prostate cancer (PCa), which is also a common cancer in men. It's still a serious health problem, even though the treatment is improving. The androgen receptor (AR), a nuclear receptor for steroid hormones, is a transcription factor that is ligand dependent. Small-molecule drugs targeting AR have been shown to contribute to the treatment of PCa. These drugs inhibit the growth of PCa cells by blocking or regulating the AR signaling pathway and inhibiting the binding of androgens (such as testosterone or dihydrotestosterone) to receptors. In this paper, the principle of AR signaling pathway in PCa and mature drugs, including abiraterone and bicalutamide, was discussed. The clinical application, efficacy, and limitation of castration-resistant prostate cancer (CRPC) were also analyzed. Through the in-depth discussion of PCa treatment of small and medium-molecule drugs and its underlying principles, this paper provides a theoretical basis for more accurate and effective treatment programs in the future.

Keywords: Prostate cancer, Small-Molecule Drugs, Androgen Receptor, Abiraterone acetate, Bicalutamide.

1. Introduction

Prostate cancer (PCa), also known as the epithelial malignant tumor of the prostate, primarily affects individuals under the age of 55. PCa ranks as the fourth most prevalent cancer globally, the second most frequent cancer, and the fifth leading cause of death in males [1]. In Europe, PCa is the most commonly diagnosed cancer because a high-fat diet is positively associated with PCa incidence, especially in Western countries [2, 3]. Hence, in many European countries like Germany, Spain, Italy, and the United Kingdom, the burden of direct initial medical costs for non-skin-related male cancer PCa is considerable [3]. Several treatment strategies have demonstrated effectiveness in enhancing the survival outcomes of patients with prostate cancer in clinical settings. The strategy chosen may rely on the cancer stage when it was diagnosed, tumor features, age, available medical facilities, attending physicians, and patient preferences [3]. Patients who are not candidates for surgery or who have a longer life expectancy, but experience treatment-related problems can benefit from radiation therapy. Patients with symptomatic localized tumors and those with locally progressed and extensive illness may consider hormone therapy [3]. Chemotherapy works well for tumors that don't respond to hormones; these tumors usually have advanced symptoms [3]. Nausea and vomiting are among the most dreaded adverse effects of chemotherapy for cancer patients [4]. In addition, additional gastrointestinal adverse effects of cancer treatment are commonly experienced by patients. For example, localized ulcers and pain can result from both oral and gastrointestinal mucositis, which can then induce anorexia, malabsorption, weight loss,

anemia, lethargy, and an increased risk of sepsis [4]. Neutropenia is a prevalent symptom in individuals receiving chemotherapy for advanced prostate cancer, it frequently results in negative consequences [5]. In recent years, small-molecule drugs have gradually become an important means to treat PCa as a new therapeutic method. Advances in therapeutic approaches, from cytotoxic clinical chemotherapy to small-molecule drugs, can successfully extend the life span of patients. This has been shown in many patients. Particularly for drugs targeting Androgen receptor signaling pathways [6]. Abiraterone is an oral inhibitor of the cytochrome P450 c17 enzyme complex, essential for androgen synthesis. In a clinical trial conducted between April 28, 2009, and June 23, 2010, a total of 1,088 patients were randomized into two groups: one receiving a placebo and the other receiving abiraterone with prednisone. Results from the trial showed a significant therapeutic benefit in the abiraterone group, although some patients discontinued treatment due to side effects or disease progression. This review aims to systematically explore the small-molecule drugs that target the androgen receptor (AR) signaling pathway for PCa treatment, with a focus on the mechanism of action, clinical application, and several specific types of drugs.

2. Androgen receptor (AR) signaling pathway in Prostatic Cancer

AR is a multifaceted protein consisting of various discrete domains that govern gene transcription. The core structure has four principal domains, including the N-terminal domain (NTD), the hinge domain, the DNA-binding domain (DBD), and the ligand-binding domain (LBD) [7]. When androgens, such as testosterone and dihydrotestosterone, bind to the ligand-binding domain (LBD), AR activity is activated. This activation regulates the expression of genes responsive to androgens, including prostate-specific antigens [7]. Each domain engages with diverse chemical components and executes particular roles, allowing AR to facilitate a broad spectrum of physiological processes. One of the key elements in PCa progression is the AR signaling pathway. Cancer-associated fibroblasts (CAFs) affect cancer start, progression, and metastasis through many methods. AR signaling in CAFs has been demonstrated to diminish the expression of several cytokines, such as CCL2 and CXCL8, which are linked to enhanced migration of PCa cells [8]. The findings indicate that androgen receptor activation in cancer-associated fibroblasts directly influences PCa cell migration via paracrine pathways [8].

The primary ligand of the androgen receptor (AR) is testosterone, which, upon binding, induces various physiological effects. Dihydrotestosterone (DHT), a more potent form of testosterone produced in the body, binds to the AR's LBD with higher activity. When DHT attaches to AR, it leads to the discomposition of heat shock proteins (HSPs) from the receptor, leading to the formation of an AR dimer. This dimer then translocates into the nucleus, where the DBD of AR identifies and adheres to AREs on DNA. Depending on the context, AR recruits co-regulatory proteins that either activate or suppress the transcription of target genes, such as prostate-specific antigen (PSA) (Figure 1). The AR signaling pathway is regulated by a negative feedback mechanism, which can be triggered by overactivation. In prostate cancer treatment, androgen deprivation therapy (ADT) works through lower androgen levels or inhibiting AR activity. For instance, abiraterone blocks androgen synthesis, while enzalutamide prevents androgens from binding to AR. In castration-resistant prostate cancer (CRPC), tumors continue to rely on AR signaling, even under reduced androgen levels. Approximately 30% of CRPC cases exhibit AR gene amplification, which is thought to contribute to resistance against AR signaling inhibitors (ARSI). PCa may regain sensitivity to androgen therapy with prolonged treatment. Testosterone modulates cell division, tumor development, and possibly cancer spread. These may be advantageous in androgen deprivation (AD) therapies when extensive surgery is unfeasible [9]. Androgens are essential in promoting prostate cancer during its initial phases. CRPC denotes a phase in which the disease advances or recurs despite diminished testosterone levels resulting after gonadectomy [9]. CRPC progression is associated with the amplification, mutation, and activation of alternate proliferative signaling pathways in AR genes, enabling cancer cells to persist in growth despite diminished androgen levels. These methods underscore the intricacy of androgen signaling in CRPC. Moreover, alterations in gonadotropin-releasing hormone receptor (GnRH-R) expression in PCa cells correlate with androgen sensitivity, especially in castration-resistant individuals [9]. Research indicates

that elevated Gleason scores correspond with diminished GnRH-R expression levels, which is associated with resistance to GnRH analog therapies in CRPC patients exhibiting high Gleason scores. This discovery corresponds with the function of androgen signaling in the advancement of PCa. A recently identified AR-specific coregulator, melanoma antigen gene protein A11 (MAGE-11), is expressed solely in humans and non-human primates [10]. MAGE-11 enhances AR transcriptional activity by interacting directly with AR and coactivators, with its expression rising as prostate cancer progresses to castration-resistant growth. The MAGE-11 gene, part of the cancer/testicular antigen X-linked MAGE gene family, is located on the Xq28 region of the human X chromosome [10]. Under low androgen levels, MAGE-11 stabilizes AR and is crucial for forming transcriptional complexes that facilitate AR-mediated gene activation.

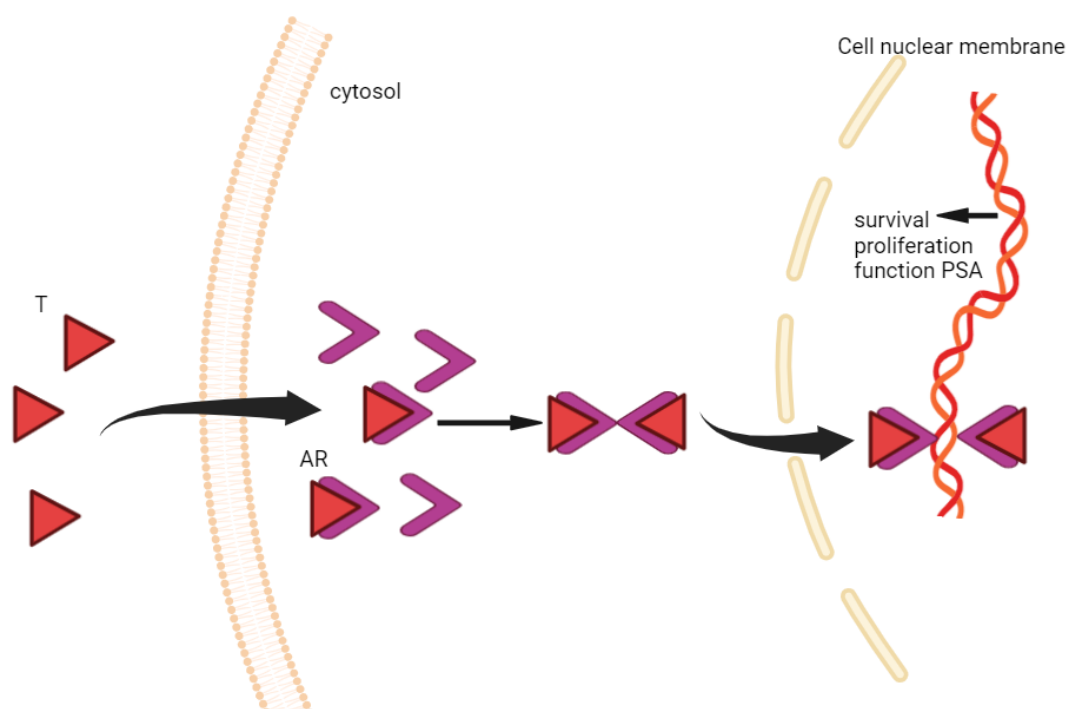


Figure 1. Graphical representation of the AR signaling pathway. **T** denotes testosterone, **PSA** stands for prostate-specific antigen, and **AR** stands for androgen receptor.

3. AR Targeting Drugs Approved for PCa Therapy

Abiraterone acetate is a famous and important medication in the treatment of metastatic CRPC, often administered alongside prednisone or methylprednisolone. Approved by the FDA, this drug is utilized for patients who do not respond to therapies aimed at lowering testosterone levels, as well as for high-risk cancer patients who are sensitive to reduced testosterone levels. The combination of abiraterone acetate and prednisone is commonly employed in managing metastatic CRPC. Abiraterone acetate selectively inhibits androgen production in prostate cancer cells, effectively delaying tumor growth by lowering androgen levels [10]. Prednisone serves as a steroid medication that can help replenish hormone levels, mitigate the adverse effects of abiraterone acetate, and improve the overall feeling and the length of life for patients, as androgen suppression may lead to adrenal insufficiency. The combination of abiraterone acetate and prednisone has been shown to significantly enhance progression-free survival and other clinical outcomes, particularly in patients with BRCA1/2 gene mutations [10]. This combination therapy may not only extend radiographic progression-free survival but also reduce the time to symptom progression and the initiation of cytotoxic chemotherapy. Treatment regimens that incorporate both medications have demonstrated good safety and efficacy in front-line patients, highlighting the importance of identifying patients with specific molecular subtypes. Bicalutamide is an FDA-approved medication that is used to treat metastatic PCa and is frequently used in combination

with agonists that release luteinizing hormone (LHRH). While the specific indications for bicalutamide are well-established, ongoing studies and clinical trials continue to explore its efficacy and applications. It is crucial to emphasize that drug information is intended for educational purposes, and patients should consult a healthcare professional for advice regarding their individual conditions. As a non-steroidal anti-androgen, bicalutamide effectively blocks AR activity and tumor development in androgen-responsive PCa. It is frequently employed as a standard treatment for locally advanced, non-metastatic PCa [11]. But some factors, such as AR mutations and the presence of coactivators, like TIF2, can contribute to drug resistance. Additionally, the decrease of AR binding and adverse reactions to decrease the level of endogenous androgens are related to decreased efficacy. Notably, patients with advanced prostate cancer who have AR variants created by selective mRNA splicing or chromosomal rearrangement, in particular, AR-V7 are more resistant to enzalutamide and abiraterone [11]. Recent studies illustrate niclosamide, which targets AR-V7, can resensitize bicalutamide-resistant cells. Furthermore, nicodamid and bicalutamide together show promise in preventing the development of enzalutamide-resistant tumors, indicating a viable approach to treating prostate cancer resistance.

4. Summary

The role of small-molecule drugs in prostate cancer treatment is becoming increasingly significant, particularly in targeting androgen receptor (AR) signaling pathways. Agents such as bicalutamide, enzalutamide, and abiraterone have proven a remarkable usage in treating both hormone-sensitive and CRPC. These drugs effectively inhibit AR activity, block androgen synthesis, and alter AR signaling, thereby slowing tumor growth and enhancing patient outcomes. Current research is heavily focused on the interactions among these various drugs, with future goals aimed at reactivating silenced pathways. This involves exploring novel therapeutic combinations, researching gene therapy targeting specific molecular subtypes, and developing innovative strategies. Future studies should concentrate on creating new targeted approaches to overcome resistance to existing therapies and further improve patient outcomes. FDA-approved small-molecule drugs offer more precise and effective options for managing prostate cancer. Although treatment strategies continue to evolve and improve, prostate cancer remains a serious health concern, necessitating ongoing research to enhance prognosis and treatment outcomes.

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