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Review Article

Resistance in Prostate Cancer: Mechanisms, Challenges and Therapeutic Innovations

Nidha Shapoo[1*], Naveed Shapoo[2], Noella Boma[1], Vladimir Gotlieb[1]

[1]Department of Medicine, New York Medical College/Metropolitan Hospital, New York, United States of America; [2]Department of Anesthesia, Sheikh Khalifa Medical City, Ajman, United Arab Emirates

ABSTRACT

Prostate cancer is the most frequently diagnosed malignancy and the second primary cause of cancer-related mortality among males in the United States and other Western nations. Androgen Deprivation Therapy (ADT) has served as the primary treatment for prostate cancer for several decades; however, the disease ultimately advances after a 2-3 years' remission, resulting in Castration-Resistant Prostate Cancer (CRPC). Not withstanding progress in diagnostic techniques and therapeutic alternatives, resistance to treatment remains a considerable obstacle in disease management. This article examines the mechanisms of treatment resistance in prostate cancer and investigates different approaches to surmount these obstacles, including innovative treatment approaches as well as personalized medicine.

Keywords: Prostate cancer; Treatment; Resistance; Strategies; Disease management

INTRODUCTION

Prostate cancer is the second most prevalent cancer among males, with those over 65 years of age facing the greatest risk [1]. Approximately 1 in 8 men may receive a diagnosis of prostate cancer at some point in their lives. The risk of prostate cancer is elevated in African American males and Caribbean men of African descent compared to men of other races [2]. The five-year survival rate for prostate cancer exceeds 98%, as over 70% of patients are diagnosed at a localized stage. The primary treatment for localized disease is radical prostatectomy and radiation therapy [3]. Upon the emergence of metastatic disease, the prognosis is generally dismal, with a 5 years' survival rate of merely 30% [4]. Prostate cancer relies on androgen receptor signaling for its sustained proliferation.

REVIEW OF LITERATURE

Androgen receptor signaling in prostate cancer

The Androgen Receptor (AR) signaling is essential for the normal functioning of the prostate gland and is also responsible for the progression of prostate cancer. The principal androgen hormones involved in the process are testosterone and 5α-Dihydrotestosterone (DHT) [5,6]. Upon binding to androgen hormones, the AR undergoes a conformational change, dissociates from co-regulatory proteins, translocates to the nucleus, dimerizes and subsequently binds to androgen response elements. This leads to cellular proliferation, apoptosis, migration, invasion and differentiation.

Throughout the progression from benign to malignant cells and low-grade to high-grade malignancy, stromal cells undergo structural and genetic alterations accompanied by a gradual decline in AR expression. The etiology of this decrease in AR expression remains unclear [7].

ADT constitutes the fundamental approach for the systemic treatment of metastatic disease, with the therapeutic arsenal having advanced considerably to incorporate chemotherapy and novel antiandrogenic treatments for metastatic Castrate-Sensitive Prostate Cancer (mCSPC). ADT may include Luteinizing Hormone-Releasing Hormone (LHRH) agonists, LHRH antagonists, or bilateral orchiectomy. In advanced disease, treatment is contingent upon the disease volume and associated

Correspondence to: Nidha Shapoo, Department of Medicine, New York Medical College/Metropolitan Hospital, New York, United States of America, E-mail: nidha.shapoo@gmail.com

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risk [8,9] (Figure 1). For individuals with high-volume and high-risk disease, triplet therapy comprising ADT, chemotherapy and Androgen Receptor Signaling Inhibitors (ARSIs) is recommended. For some patients, doublet therapy combining ADT with any alternative medicines is preferred. ARSIs comprise abiraterone acetate, a specific inhibitor of steroid 17α-hydroxylase (CYP17A1) and androgen receptor antagonists such as enzalutamide, apalutamide and darolutamide. Recent studies indicate enhanced survival in mCSPC with doublet or triplet therapy [10-13] (Figure 2).

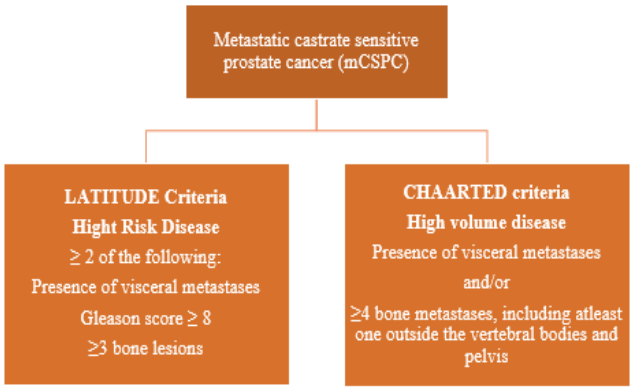

Figure 1: Definition of high risk/high-volume disease.

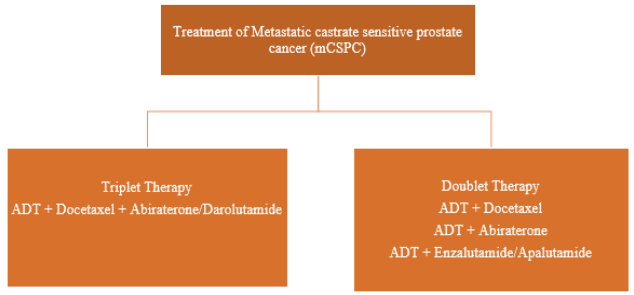

Figure 2: Treatment of metastatic Castrate Sensitive Prostate Cancer (mCSPC).

Nonetheless, despite these considerable advancements, prostate cancer continues to be a predominant cause of cancer mortality worldwide. Prostate cancer is a highly varied disease and its growth over time results in the emergence of androgen deprivation therapy resistance, known as Castrate-Resistant Prostate Cancer (CRPC). CRPC is characterized by disease development despite androgen deprivation therapy and testosterone levels below 50 ng/dl. Multiple factors contribute to treatment resistance, including AR gene amplification, AR gene mutations, variable forms of AR, alternative signaling pathways and the tumor microenvironment.

Comprehending the mechanisms underlying treatment resistance is essential for formulating appropriate methods to address this significant challenge in prostate cancer care (Figure 3).

Figure 3: Mechanisms of treatment resistance in prostate cancer.

MECHANISMS OF TREATMENT RESISTANCE

Androgen receptor gene amplification

Amplification of the AR gene, resulting in heightened AR expression, is a common cause of resistance to anti-androgens. AR gene amplification has been documented in 17%-57% of pre-treated metastatic CRPC (mCRPC), contingent upon the therapy used [14,15]. Isolated Circulating Tumor Cells (CTCs) from mCRPC patients exhibiting resistance to abiraterone or enzalutamide demonstrated AR gene amplifica- tion in 50% of cases [16].

Androgen receptor gene mutations

AR gene alterations manifest in 10%-20% of CRPCs, predominantly as single-base substitutions resulting from somatic mutations rather than germline mutations. Most of these mutations occur in the androgen receptor Ligand-Binding Domain (LBD), while others emerge in the N-Terminal Domain (NTD) and the DNA-binding domain [17]. Point mutations in the androgen receptor Ligand-Binding Domain (LBD) provide resistance to anti-androgen therapies [18,19]. These changes modify the binding affinity of ligands, leading to varied activation by antiandrogens and steroids [20]. A meta-analysis conducted by Snaterse et al., indicated that the most frequent mutations in CRPC are *L702H*, *W742L/C*, *H875Y*, *F877L* and *T878A/S* [21]. The AR, *F876L* and *F876L/*T877A point mutations convert Enzalutamide from an AR antagonist to an AR agonist, while the mutations AR, W741C, *T877A*, *W741L*, *W741C/T877A*, *F876L*, *F876L/T877A* and L701H can transform Bicalutamide from an AR antagonist to a powerful AR agonist, resulting in the reactivation of AR signaling [22].

AR mutations can be identified in CTCs with equivalent concordance to tissue biopsy [23].

Androgen receptor splice variants

The production of AR splice variants, which lack the LBD, represents an alternative mechanism of treatment resistance. At least 22 Androgen Receptor Variants (AR-Vs) have been identified, with AR-V3, AR-V7/AR3, AR-V9 and ARV567es now detectable in blood or tissue samples linked to CRPC [24,25]. AR-V7 is the most extensively researched variant and significantly contributes to treatment resistance. The mechanisms underlying the production of AR-Vs involve abnormal RNA splicing and intragenic rearrangements of the AR gene [26]. Numerous research has investigated the function of AR-Vs as prognostic and predictive biomarkers for resistance to AR-targeted treatments, including abiraterone and enzalutamide. AR-Vs are linked to advanced disease, reduced Progression-Free Survival (PFS) and indicate resistance to abiraterone and/or enzalutamide [27-34].

Androgen receptor independent signaling pathways

De-differentiation to AR-negative disease transpires during prostate cancer growth because of cellular rewiring processes and plasticity, mostly driven by mutations, particularly the concurrent loss of the tumor suppressors RB1 and TP53 [35,36]. The introduction of ARSI drugs such as enzalutamide and abiraterone lead to the increased prevalence of AR-negative tumors in patients with mCRPC from 11%-36% [37]. Some variants of AR-negative disease, encompassing Neuroendocrine Prostate Cancer (NEPC) and the double-negative subtype, are characterized by the absence of both AR and neuroendocrine markers [38,39]. The activation of the Wnt/β-Catenin signaling pathway has been shown to promote neuroendocrine trans-differentiation. The prevalence of AR double-negative cancers has escalated from 5% to over 20% due to novel AR inhibitors through FGF signaling and Mitogen-Activated Protein Kinase (MAPK) pathway activation [39]. Labrecque et al., delineated five unique subtypes of mCRPC predicated on RNA expression of AR and dominant neuroendocrine markers: AR-high tumors, AR-low tumors, amphicrine tumors displaying both AR and NE marker expression, double-negative tumors and tumors exhibiting small cell and NE characteristics absent of AR expression [40].

The PI3K/AKT/mTOR signaling pathway is aberrantly regulated in all instances of advanced prostate cancer. The AR and PI3K/AKT signaling pathways are regulated by a reciprocal feedback mechanism. Multiple studies have confirmed the role of the PI3K/AKT/mTOR signaling pathway in the development of treatment resistance and tumor progression [41].

Hypoxia and hypoxia-inducible factors HIF1a are linked to the development of resistance to androgen-targeted therapy and the advancement to CRPC. Androgen deprivation therapy under hypoxic settings increases androgen receptor independence and confers resistance to androgen/androgen receptor-targeted therapies [42-44].

Alterations in Homologous Recombination Repair (HRR) pathways occur in about 20% of advanced or metastatic prostate cancer, resulting in compromised DNA repair [45]. Individuals with *BRCA2* pathogenic variants demonstrate elevated serum PSA levels at diagnosis, a greater incidence of high Gleason tumors, increased risk of metastases and recurrence rates and enhanced resistance to prostate cancer therapies [46]. The JAK-STAT signaling pathway is active in CRPC, promoting stem cell plasticity and the development of cancer stem cell phenotypes. In mCRPC with TP53/RB1 deletion and *SOX2* overexpression, JAK-STAT signaling promotes lineage plasticity, fueled by resistance to AR-targeted treatments [47].

Tumor Microenvironment (TME)

The Tumor Microenvironment (TME) plays a major role in the emergence of resistance. The TME comprises fibroblasts, pericytes, immune cells, endothelial cells and vascular endothelial cells, all of which can engage with cancer cells in diverse and dynamic ways. The non-cellular components include the Extracellular Matrix (ECM), inflammatory mediators, chemokines and matrix enzymes which promote tumor growth and progression by altering intercellular signaling [48]. Cancer-Associated Fibroblasts (CAFs) are among the most abundant elements in the TME, affecting the malignant phenotype at all levels. Prostate cancer has considerable variety. The interaction between prostatic epithelial cells and the tumor microenvironment generates complex changes in the adjacent stromal components, worsening disease severity, increasing metastatic potential and providing resistance to conventional therapy [49-51]. Neural tissue has been identified as an active component of the tumor microenvironment in prostate cancer. Perineural Invasion (PNI) is the most recognized type of cancer-nerve interaction in prostate cancer. Research has demonstrated the significance of axonogenesis, neurogenesis and the perineural niche in creating a conducive microenvironment for the survival and proliferation of cancer cells [52,53].

Over-expression of multidrug transporter *ABCB1*/P-glycoprotein (p-gp)

Multidrug transporter *ABCB1* is an efflux transporter that reduces the intracellular levels of chemotherapeutic agents. The ineffectiveness of taxane therapy is often associated with the overexpression of *ABCB1* which is mostly induced by taxane-based treatment. Decreased *ABCB1* expression was seen in prostate cancer tissue samples from chemotherapy-naïve patients, suggesting acquired resistance [54,55].

Sphingolipid gene aberrations

Sphingolipids are a class of lipids characterized by a sphingosine backbone, which regulates various biological processes, including cellular proliferation and inflammation. Research by Lin et al., established an association between the ceramide-Sphingosine-1-Phosphate (ceramide-S1P) signaling axis and resistance to ARSI in mCRPC, particularly in cases with androgen receptor amplification [55]. Elevated circulating ceramide levels and anomalies in androgen receptors were associated with inferior clinical outcomes [55].

Strategies to overcome treatment resistance

Strategies to overcome treatment resistance are:

Novel AR inhibitors: Darolutamide is an innovative androgen receptor inhibitor that antagonizes mutant androgen receptors (F877L and T878A), which confer resistance to enzalutamide and apalutamide [56]. Darolutamide received FDA approval in 2019 to manage nonmetastatic CRPC [57]. Phase 3 clinical trials have demonstrated that darolutamide substantially extends metastasis-free survival in high-risk nonmetastatic CRPC [58].

AR degraders: Due to the elevated stability of AR proteins in CRPC cells, the effectiveness of AR antagonists is diminished; nevertheless, AR degraders can mitigate this resistance [59]. The Proteolysis-Targeting Chimera (PROTAC) has evolved as a sophisticated method to degrade AR by exploiting the ubiquitin–proteasome system. At present, only ARV-110 and ARV-766 have advanced to phase II clinical trials as AR PROTACs. ARV-110 (bavdegalutamide), an orally accessible AR PROTAC, is currently the most advanced PROTAC in phase II clinical trials for CRPC [60]. Phase II clinical data demonstrated its effectiveness in patients with T878X and H875Y mutations [61].

Combination therapies

Integrating therapies may enhance treatment efficacy and overcome resistance by simultaneously targeting multiple pathways.

Poly (ADP-ribose) Polymerase (PARP) inhibitors, including Olaparib and Rucaparib, combined with abiraterone or enzalutamide, have shown a survival benefit in mCRPC by improving progression-free and overall survival rates. Both are FDA-approved for the treatment of metastatic castration-resistant prostate cancer with deficient homologous recombination repair pathways [62,63]. Rucaparib is authorized for patients with BRCA1/2 mutations who have previously undergone ARSI therapy and taxane-based chemotherapy [64]. Olaparib has been authorized for an extended spectrum of HRR genes and does not require prior treatment with taxane-based chemotherapy [64]. Numerous clinical trials are presently examining the efficacy of new PARP inhibitors, both as standalone treatments and in conjunction with other drugs, in CRPC.

The combination of chemotherapeutic drugs, such as carboplatin with docetaxel, in patients whose disease has progressed on docetaxel monotherapy has demonstrated modest advantages. Approximately 20% of patients experienced delayed disease progression of about 3 to 6 months and a drop in PSA levels of ≥ 50%; nevertheless, no level 1 evidence supports the utilization of platinum-based therapies in this context [65].

Angiogenesis inhibitors combined with chemotherapy demonstrated good outcomes in preclinical investigations; nevertheless, their success was only moderate [66]. A comprehensive understanding of angiogenesis and its regulatory signaling pathways is essential for the development of innovative, tailored antiangiogenic treatments in prostate cancer [67].

Immunotherapy

Utilizing the immune system to specifically target prostate cancer cells constitutes a potential strategy. Strategies may encompass cancer vaccines, immune checkpoint inhibitors and adoptive cell therapies that augment the body's capacity to combat cancer.

Sipuleucel-T (S-T), an autologous cellular immunotherapy, is a therapeutic cancer vaccine that demonstrated an increase in median overall survival for patients with mCRPC in a phase III trial [68].

Immune Checkpoint Inhibitors (ICIs) have demonstrated ineffectiveness in prostate cancer, which is regarded as an immunologically "cold" malignancy due to its highly immunosuppressive tumor microenvironment, reduced T-cell infiltration and diminished mutation burden [69]. A subset of patients exhibiting elevated PD-L1 tumor expression, CDK12 mutations, high tumor mutational burden, or tumors characterized by high Microsatellite Instability (MSI) and Mismatch Repair Deficiency (dMMR) has recently shown remarkable responses to ICIs and/or their combinations with other agents [70]. Consequently, immunotherapy continues to be an attractive treatment modality for prostate cancer to enhance disease control [71]. Multiple phase 3 clinical trials are currently assessing the efficacy of pembrolizumab in conjunction with docetaxel, enzalutamide and olaparib [72].

Prostate-Specific Membrane Antigen (PSMA) has emerged as an optimal target for innovative prostate cancer treatment, either by the radiolabeling of PSMA ligands for radionuclide therapy or by using immunotherapeutic strategies to target PSMA. In a phase III trial, PSMA Radioligand Therapy (PRLT) demonstrated a survival advantage in mCRPC compared to optimal supportive care or standard treatment [73].

PSMA-targeted immunotherapy is categorized into four primary types: Antibody-Drug Conjugates (ADC), Chimeric Antigen Receptor T-cells (CAR-T), PSMA-directed vaccinations and bispecific T-cell redirected therapy. All these medicines are still undergoing clinical development; nevertheless, preliminary phase trials have demonstrated encouraging results [74-78].

Targeting signal pathways

Numerous small molecule inhibitors have been formulated to inhibit signaling pathways linked to the progression of CRPC (Table 1) [55,72,79].

The recent phase 3 CONTACT-02 trial (NCT04446117) has shown that the combination of cabozantinib and atezolizumab significantly improved PFS compared to second-line Novel Hormonal Treatment (NHT) in patients with mCRPC. The interim overall survival analysis in the intention-to-treat population likewise demonstrated an overall survival advantage in the cabozantinib group [80].

Table 1: Clinical trials of small molecule inhibitors in targeting the signaling pathways in CRPC.

Drug	Target	Phase	NCT identifier
Samotolisib (LY3023414)	PI3K	2	NCT02407054
Perifosine (KRX-0401)	AKT	2	NCT00060437
Ipatasertib (GDC-0068)	AKT	3	NCT03072238
Ridaforolimus (MK8669)	mTOR	2	NCT00777959
Temsirolimus (CCI-779)	mTOR	2	NCT00919035
Sapanisertib (MLN0128)	mTOR	2	NCT02091531
Bevacizumab	VEGF-A	3	NCT00110214
Cetuximab	EGFR	2	NCT00728663
Dovitinib (TKI258)	FGFR, VEGFR, PDGFR	2	NCT01741116
Cabozantinib (XL184)	VEGFR, c-MET, c-KIT	3	NCT01605227
Masitinib (AB1010)	KIT, PDGFR, FGFR	3	NCT03761225
Dasatinib (BMS-354825)	SRC, c-KIT	3	NCT00744497
Opaganib	Sphingosine kinase	1	

Overcoming *ABCB1*/P-glycoprotein (p-gp) multidrug resistance/drug repurposing

This resistance can be surmounted through novel *ABCB1* inhibitors and the repurposing of FDA-approved medications exhibiting *ABCB1* inhibitory properties [81-83]. Despite the unsatisfactory clinical responses associated with the discovery of p-glycoprotein inhibitors, this area of study holds promise for the future [82]. Drug repurposing, the application of existing medications originally designed for different ailments, is both cost-effective and efficient since it leverages pharmaceuticals that have already established safety and efficacy. Numerous medications prescribed for alternative disorders have demonstrated efficacy in targeting the channels utilized by CRPC. Most trials have concentrated on Metformin, either as a monotherapy or in conjunction with other treatments, in advanced prostate cancer, yielding encouraging outcomes. Numerous clinical trials have been developed to repurpose medications for the treatment of prostate cancer [83].

Novel therapies

Lorigerlimab is a dual inhibitor of Cytotoxic T-Lymphocyte-Associated Protein 4 (CTLA-4) and Programmed Death-1 (PD-1) that has shown a response rate of 25.7% in chemorefractory mCRPC [84].

BPX-601 is an autologous CAR-T cell immunotherapy targeting Prostate Stem Cell Antigen (PSCA) that has demonstrated encouraging outcomes in a phase 1 multicenter trial [85].

In a phase III trial, Capivasertib, a selective inhibitor of AKT1/2/3, combined with docetaxel, demonstrated an increase in overall survival among patients with mCRPC [86].

Personalized/precision medicine

Prostate cancer is a diverse disease marked by considerable genetic variability. Utilizing genomic profiling to identify mutations and alterations in certain malignancies can facilitate personalized treatment approaches. Concentrating on routes based on genetic composition may improve outcomes in resistant situations [87].

CONCLUSION

Treatment resistance in prostate cancer is a complex challenge, necessitating a thorough comprehension of the underlying mechanisms. Utilizing combination therapy, targeting the tumor microenvironment and signaling pathways, adopting personalized medicine and investigating innovative therapeutic agents may enhance results for patients with treatment-resistant prostate cancer. Continued research and clinical trials will be essential in developing successful solutions to address this intricate condition.

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