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Recent Advances in Advance Prostate Cancer

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Abstract

Prostate cancer being the second most frequent and fifth leading cause of mortality has led to conduct of many new clinical trials and development of newer therapeutic agents. In the last decade with better understanding of biology of disease there is dramatic improvement and sea change in survival outcomes in advanced prostate cancer with advent of chemotherapy, targeted therapy immunotherapy besides androgen deprivation therapy. Varied newer drugs and combinations in recent years have improved the outcome of prostate cancer in terms of both overall survival(OS) and metastases free survival(MFS). Some of the latest drugs which have cleared regulatory approval are Abiraterone, Enzalutamide,Apulatamide, Sipuleucel-T etc. However still more needs to be explored to negate and overcome the resistant mechanisms. Here in this article we have summarized the varied newer and recent developments in advanced prostate cancer.

Key words prostate cancer, survival, androgen deprivation therapy, immunotherapy, targeted therapy

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Introduction

As per World Health Organization (WHO) data of 2020, prostate cancer was the 3rd most common cancer (around 7%) after lung (around 11%) and colorectal cancer (around 10%) [1]. In India, it is the second most common malignancy in the population based cancer registries of Delhi, Kolkata, Pune, and Thiruvananthapuram, and third most common in Mumbai and Bangalore [2]. Death rates for prostate cancer have been decreasing in many countries like United States and Europe including developed countries of Asia [1]. This is attributed to earlier diagnosis because of robust screening as well as improved and recent advances in treatment for advanced prostate cancers.

Prostate being a slow goring tumor, therapeutic modalities in localized and organ confined prostate cancer are- either surveillance or localized treatment in form of surgery or radiotherapy depending on expected patient survival and risk stratification grouping as seen in **Table 1**. Risk stratification is based on varied parameters such as clinical Tumor (T) stage as in **Table 2**, laboratory features like pre-treatment Prostate Specific Antigen (PSA) levels and PSA density and pathological features such as prostatic biopsy and histological grade groups respectively. Histologic grade is determined form Gleason score and Gleason pattern (**Table 3**).

Moreover, with advent of newer molecular classification, it may soon supplant the older risk stratification in prostate cancers as the newer genomic method would seem to be a much better approach in guiding surveillance versus insinuation of early treatment.

In patients with localized disease with intermediate and high risk features aim is eradication of tumor locally and at the same time elimination of micro metastases if any. However, for patient with advance disease where disease has spread to distant organs or nodes (regional or non-regional) and also for CRPC, the aim is to improve quality of life and also prolong life by eliminating debilitating symptoms and prevention of symptoms. Over the last decade numerous newer agents have developed for management of advanced and metastatic prostate cancer and we will be focusing on these newer therapeutic modalities here.

Treatment strategy in prostate cancer

The Nobel prize-winning research by Huggins and many other studies indicate that prostate cancer is driven by androgen receptor (AR). In 1940, Huggins and Hodges showed that in patients with prostatic cancer with marked elevation of acid phosphatase, castration or injection of large amounts of estrogen reduced the level of acid phosphatase in the blood, thereby resulting in tumor regressions and helped in palliating symptoms of the disease [3]. Surgical castration was considered the gold standard till 1980s when it was superseded by Luteinizing hormone- releasing hormone (LHRH) agonists. Then came the era of "combined androgen blockade(CAB)" and in 1982 non-steroidal antiandrogen flutamide was combined with LHRH agonists in an attempt to increase the degree of AR signaling inhibition and thereby response [4]. LHRH agonists were also combined with adrenal androgen synthesis inhibitors but none of the approaches for CAB resulted in longer survival than conventional castration as can be seen in the meta analysis carried out by prostate cancer trialist collaborative group [5]. With the introduction of systemic therapy, docetaxel in 2004 there is sea change and considerable improvement in quality of life(QoL) and progression free survival (PFS) for men with metastatic castration- resistant prostate cancer (mCRPC).

In advanced prostate carcinoma where disease has progressed outside prostate, androgen deprivation therapy (ADT) plays a major role. Unfortunately, in advanced prostate cancers, most patients develop resistance to ADT and progress towards castration-resistant prostate cancer (CRPC) after 18 to 36 months [6]. CRPC is prostate cancer with clinical, radiographical and biochemical progression despite castrate levels of serum testosterone (<50ng/dl; 1.7nmol/L) [7]. This level was determined based on methodological considerations and the sensitivity of assays that were available during the early 2000s [8]. However several studies since the early 1990s have challenged the outdated benchmark of 50ng/dl and recommended revisiting the definition, with many suggesting a new benchmark of 20ng/dl;0.7 nmol/L [9]. Though these recommendations have been made, but are not yet clinically confirmed by the National Comprehensive Cancer Network (NCCN) and the castrate level considered by the regulatory authorities is still < 50 ng/dL (1.7 mmol/L).

Better understanding of the biology of disease has led to the accelerated development of newer treatments such as- biological agent (Sipuleucel-T), cytotoxic agent(Cabazitaxel), hormonal agents(CYP17 inhibitor abiraterone acetate and and a next-generation antiandrogen, enzalutamide), bone-seeking α- emitting radionuclide (radium-223) and denosumab, a monoclonal antibody that binds the cytokine RANKL (receptor activator of nuclear factor kappa B ligand).

Despite these advances, disease still relapses due to different resistant mechanism. Recent data implicate the continued activation of the androgen axis as a stimulus for growth for CRPC. Moreover, xenograft studies have too confirmed the central role of increased AR expression in CRPC development [10]. Hence different survival and growth promoting pathways which interact with AR signaling needs to be targeted.

Hence, in this study we are focusing on newer agents that have been approved since 2010 to treat CRPC along with other ongoing newer developments in advanced prostate cancer.

Newer Potential therapies in advanced prostate cancer

Drugs targeting Androgen Receptor pathway (Secondary Hormonal Therapy)

(a) Androgen Biosynthesis Inhibition: Observation by Tilki and Evans that androgen axis remains active in patients even with CRPC and that metastatic prostate cancers can generate its own androgens has led to the development of agent that can impact androgen production in tumor as well as other sites in the body. The first such agent approved for mCRPC is abiraterone [11]. Prostate cancer is a testosterone dependent disease with pulsatile release of luteinizing hormone releasing hormone (LHRH) after hypothalamus receives a signal. LHRH subsequently releases luteinizing hormone (LH) which then activates leydig cells in testes to produce testosterone. The alternate steroid pathway also exists and it is via the adrenal gland. Gonadotropin-releasing hormone (GnRH) and LH regulates testicular androgen synthesis whereas corticotrophin-releasing hormone (CRH)-adrenocorticotropic hormone(ACTH) axis regulates adrenal androgen synthesis. The androgen signalling axis pathway and the drugs and enzymes inhibiting both testicular and adrenal steroid production is depicted in **Figure 1** [12]. Abiraterone inhibits Cytochrome P450 17α-hydroxylase(CYP17), the enzyme involved in androgen synthesis. Other non-steroidal antiandrogens like biclutamide, flutamide, and nilutamide competitively inhibit the binding of androgens to androgen receptors and enzalutamide, another non-steroidal antiandrogen blocks the translocation of the ligand bound AR complex to the nucleus and from binding to DNA.

Abiraterone is an irreversible inhibitor of CYP17A1, a 17–20 lyase and 17- α hydroxylase of the cytochrome P450 family, that blocks androgen production in the testis, adrenal glands and prostate,

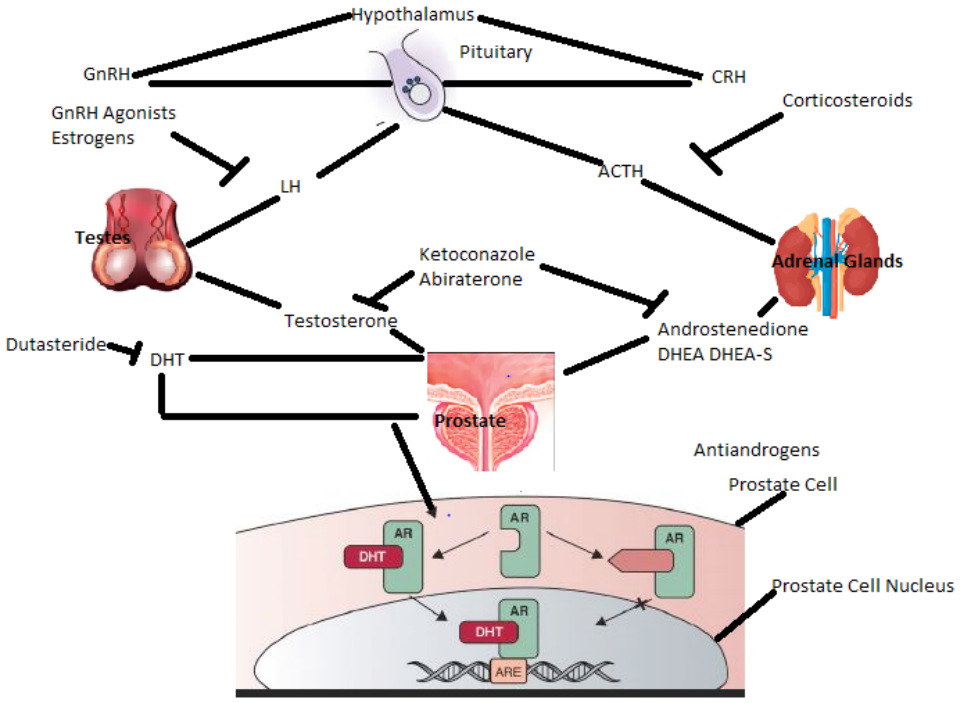

Figure 1. The Androgen Signaling axis with its inhibitors. GnRH: Gonadotropin-releasing hormone; LH: Luteinizing hormone; CRH: Corticotrophin releasing hormone; ACTH: Adrenocorticotropic hormone; DHEA: Dehydroepiandrosterone; DHEA-S: Dehydroepiandrosterone sulfate; DHT: Dihydrotestosterone; AR: Androgen receptor; ARE: Androgen response element.

thus preventing prostate cancer growth. It has antitumor effects on both chemotherapy treated and chemotherapy naïve patients with CRPC. In April 2011 Food and Drug Administration (FDA) approved abiraterone in combination with low dose prednisone for metastatic CRPC patients who have received docetaxel based on the results of phase III trial COU-AA-301 [13]. FDA in 2012 also approved it for pre-docetaxel setting based on the results of phase III trial COU-AA-302 [14]. Moreover, very recently in February 2018, FDA approved abiraterone in combination with low dose prednisone in metastatic hormone sensitive prostate cancer(mHSPC) based on the results of two phase 3 clinical trials(STAMPEDE AND LATITUDE) that demonstrated improved overall survival (OS) over ADT alone [15, 16]. Other CYP17A1 inhibitors like orteronel and galeterone were also studied but they failed to show any substantial benefit [17].

(b) Androgen Receptor(AR) Antagonist: Enzalutamide, formerly known as MDV 3100 is a second generation pure AR antagonist as unlike first generation AR antagonist such as biclutamide or flutamide it has no known agonist activity [10]. It got FDA approval in 2012 and 2014 for mCRPC with prior docetaxel therapy and for chemotherapy naïve mCRPC respectively based on phase 3 trials(AFFIRM and PREVAIL respectively [18, 19]. Moreover two other randomized clinical trials, TERRAIN study and STRIVE trial have demonstrated superiority of enzalutamide over biclutamide for cancer control in mCRPC [20, 21]. In addition, it also improves OS as well as PFS (MFS) in metastatic CRPC (mCRPC) patients and is category 1 option for patients with mCRPC as per national comprehensive cancer network(NCCN) guidelines. FDA also approved it in 2018 for non-metastatic CRPC(nmCRPC) and is category 1 option as per NCCN guidelines for nmCRPC if PSA doubling time(PSADT) is less than or equal to 10 months based on results of phase 3 PROSPER trial which showed improved metastasis free survival(MFS) [22].

Apalutamide is another oral AR antagonist resembling enzalutamide structurally and got FDA approval in 2018 for nm CRPC based on phase 3 SPARTAN trial which had improved MFS [23]. Darulotamide, another AR antagonist with low blood brain barrier penetration and thereby better safety profile got FDA approval in 2019 in nmCRPC based on phase 3 ARAMIS study which also pointed towards improved primary end point of MFS compared to placebo [24].

Traditional secondary hormonal therapy used before the introduction of above mentioned newer hormonal agents are first generation antiandrogen, antiandrogen withdrawal, steroids, ketoconazole, or estrogen such as diethylstilbestrol(DES). However, none has shown to increase survival in randomized clinical trials.

Chemotherapy (Cytotoxic Therapy)

(a) Docetaxel: Mitoxantrone was the first cytotoxic agent to get approved way back in 1996 and was indicated only in palliative setting when used in combination with prednisone. Thus it was the first cytotoxic agent which became standard to which other treatments would be compared.

Subsequently two pivotal trials (TAX 327 and SWOG 9916) which showed better palliation and delayed progression with docetaxel and prednisone combination over mitoxantrone and prednisone led to the approval of docetaxel with prednisone in mCRPC in 2004 [25]. Docetaxel also became standard of care for mHSPC based on the results from two phase 3 trials (ECOG 3805/ CHAARTED and STAMPEDE) [26, 15].

(b) Cabazitaxel: Cabazitaxel, a microtubule inhibitor just like docetaxel prevents tubulin depolymerization and thereby mitotic cell division, eventually leading to cell death [6]. It has recently been approved by FDA in June 2010 in docetaxel resistant cancers

Table 1. Risk stratification in prostate cancers.

Risk Group	Clinical	Laboratory	Pathological	Remarks	
Very Low	T1c	PSA<10ng/mL PSA density <0.15ng/mL/g	Grade Group 1 Fewer than 3 prostate biopsy fragments/ cores positive and ≤ 50% cancer in each fragment/core	Should have all the following	
Low	T1-2a	PSA <10ng/mL	Grade Group 1	Should have all of the following	
Intermediate	T2b-T2c	PSA 10-20ng/ mL	Grade Group 2 or 3	Favorable	Has all of the following: (1) 1 intermediate risk factor (IRF); (2) Grade Group 1 or 2; (3) <50% biopsy cores positive
				Unfavourable	Has 1 or more of following: (1) 2 or 3 IRFs; (2) Grade Group 3; (3) ≥50% biopsy cores positive
High	T3a	PSA >20 ng/mL	Grade Group 4 or 5	Has at least one of the following	
Very High	T3b-4	-	Primary Gleason pattern 5;>4 cores with Grade Group 4 or 5	Has at least one of the following or has 2-3 high risk features	

based on randomized phase 3 TROPIC trial [27]. The NCCN Guidelines panel has thus included cabazitaxel as second line therapy in patients with symptomatic mCRPC who has progressed on docetaxel [28].

Immunotherapy

The autologous active cellular immunotherapy, sipuleucel-T became the first in a new class of cancer immunotherapeutic agents to be approved by FDA for mCRPC in 2010 based on the 4.1 months' survival in IMPACT trial demonstrating its superiority in mCRPC [29]. However it failed to show significant improvement in time to progression or PSA decline. This discordance between progression free and OS may be observed in immunotherapy trials for prostate cancer as similar trend was noted when PROSTVAC, a PSA directed vaccine therapy, was compared to placebo in men with CRPC [10]. Prostvac is a prostate cancer vaccine regimen consisting of a recombinant vaccinia vector as a primary vaccination, followed by multiple booster vaccinations employing a recombinant fowl pox vector. Both vectors contain the transgenes for prostate-specific antigen (PSA) and multiple T-cell costimulatory molecules (TRICOM) [30].

Another recent focus of immunotherapy in CRPC is prostate specific membrane antigen (PSMA). The initial clinical study with a PSMA-targeting ADC gave positive results but no phase 3 study has been carried out till date. However only phase II studies have been completed in docetaxel refractory patients [6, 10].

Some of the trials leading to approval of these newer agents are summarized in **Table 4**.

Targeted therapy

(a) Pembrolizumab: FDA approved the use of anti PD1 antibody, pembrolizumab in May 2017 based on a study with 149 patients for patient with unresectable or metastatic microsatellite instability high(MSI-H) or mismatch repair (MMR)-deficient (dMMR) solid tumors who have progressed on prior treatment and are left with no suitable alternatives. Based on outcomes of other smaller studies and KEYNOTE-199 phase II study, NCCN panel supported the use of pembrolizumab as category 2B recommendation in patients with MSI-H or dMMR metastatic CRPC whose disease has progressed on at least one-line systemic therapy for mCRPC [28].

(b) Bone directed therapy: Most patients with CRPC have painful bone metastases. The high propensity for prostate cancers to metastasize to the bone results in significant morbidity from skeletal related events (SREs) and thereby can impact duration and Quality of Life of patients (QoL). This is further complicated by the bone loss associated with ADT and frequent use of corticosteroids. Hence, by targeting bone microenvironment, SREs can be delayed resulting in prolong and better QoL.

Zoledronic acid is the only bisphosphonate which is FDA approved for CRPC with bone metastases.

Denosumab is a fully human monoclonal antibody directed against RANKL (receptor activator of nuclear factor kappa-B ligand) and inhibits osteoclast function. Though in a phase 3 trial of 1432 patients with nmCRPC, denosumab delayed bone metastases by 4 months compared to placebo and was also statistically significant it failed to receive FDA approval for bone metastases [28].

Alpha Emitting agent, Radium 223 dichloride is a targeted alpha therapy which is administered intravenously. In CRPC patients, it significantly improved OS irrespective of prior docetaxel use and also decreased pain related to bony metastases and demonstrated a favorable safety profile. So, it was originally approved by the

Table 2. Clinical TNM staging in prostate carcinoma.

Symbols	Explanation
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Clinically inapparent tumor that is not palpable
T1a	Tumor incidental histologic finding in 5% or less of tissue resected
T1b	Tumor incidental histologic finding in more than 5% of tissue resected
T1c	Tumor identified by needle biopsy found in one or both sides but not palpable
T2	Tumor is palpable and confined within prostate
T2a	Tumor involves one-half of one side or less
T2b	Tumor involves more than one-half of one side but not both sides
T2c	Tumor involves both sides
T3	Extraprostatic tumor that is not fixed or does not invade adjacent structures
T3a	Extraprostatic extension(unilateral or bilateral)
T3b	Tumor invades seminal vesicle(s)
T4	Tumor is fixed or invades adjacent structures other than seminal vesicles such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall
NX	Regional lymph nodes cannot be assessed
N0	No positive regional lymph nodes
N1	Metastases in regional node(s)
M0	No distant metastases
M1	Distant metastases
M1a	Distant metastases to nonregional lymph node(s)
M1b	Distant metastases to bone(s)
M1c	Distant metastases to other site(s0 with or without bone disease

FDA in May 2013 for CRPC patients with bone metastases and no known visceral metastatic disease based on clinical data from phase 3 randomised trial (ALSYMPCA) [6, 28].

Beta Emitters, strontium-89(89Sr) or samarium-153(153Sm) unlike the alpha emitter radium 223 had no survival advantage and are only used in palliative setting for treatment of painful of bone metastases [28].

Targeted agents in patients with DNA repair gene mutations

There is a high incidence of DNA damage response (DDR) defects in advanced prostate cancer patients and include mainly mutations in the homologous recombination and DNA mismatch repair pathways [31]. Early studies suggest germline and somatic mutations in homologous recombination repair (HRR) genes and may be predictive of clinical benefit with poly ADP ribose polymerase (PARP) inhibitors. Presently two PARP inhibitors approved by FDA are Olaparib and Rucaparib. Both got recent FDA approval in May 2020. Olaparib got FDA approval based on favorable efficacy data from phase 3 PROfound trial for use in patients with mCRPC and deleterious or suspected deleterious germline or somatic HRR gene mutations in at least one of 14 genes (BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51c, RAD51D or RAD54L) and who had previously received treatment with enzalutamide or abiraterone. Rucaparib got accelerated FDA approval based on preliminary favorable data from TRITON 2 clinical study. It is however awaiting full FDA approval as results of phase 3 TRITON 3 study is still awaited [28].

Way ahead-what`s the future forward

Table 3. Definition of histologic grade.

Grade Group	Gleason Score	Gleason Pattern
1	≤6	≤3+3
2	7	3+4
3	7	4+3
4	8	4+4
5	9 or 10	4+5; 5+4; 5+5

Advances in our understanding of prostate cancer biology have increased the arsenal of drugs available to treat advanced prostate cancer in recent years and thereby has improved the outcomes for patients across the clinical spectrum of the disease. Despite recent advances, additional therapeutic modalities also need to be explored for even better outcomes to overcome resistance mechanisms.

The androgen receptor splice variant 7 (AR-V7) variant data in patients has now been published, confirming the importance of preclinical studies. Lack of response to enzalutamide and abiraterone in mCRPC has been attributed to detection of AR-V7 mRNA in circulating tumor cells(CTCs) using an RNA based polymerase chain reaction (PCR) assay. This AR variant does not, however, predict resistance to docetaxel in the same setting. Men with AR V7 positive CTCs exhibited superior PFS with taxanes as compared to abiraterone and enzalutamide [28]. Taken together, these data indicate that AR-V7 can function as a predictive biomarker. Larger studies are needed to confirm these initial observations.

Finally, with development of varied newer agents comes the dilemma of optimal timing and sequencing and combining one modality especially newer modalities with conventional anti androgen and cytotoxic therapies. However gradually with better understanding of the rationale of these newer agents, clinicians will eventually reap more benefit from this newer and varied arsenal of therapeutic agents.

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Table 4. Newer agents showing definite os benefit in castrate resistant prostate cancer and getting regulatory approval.

Drug name	Trial name	Control arm	HR	OS/MFS in months	P value
Abiraterone + Prednisone	Phase 3 COU-AA-302 Study [13]	Placebo +Prednisone	0.81	34.7 Vs 30.3	0.0033
Enzalutamide(post docetaxel)	AFFIRM [17]	Placebo	0.631	18.4 vs 13.6	<0.0001
Enzalutamide	PREVAIL [18]	Placebo	0.71	32.4Vs 30.2	<0.001
Apulatamide	SPARTAN [22]	Placebo	0.28	Median MFS-40.5Vs 16.2	<0.001
Darulotamide	ARAMIS [23]	Palcebo	0.41	Median MFS-40.4Vs 18.4	<0.001
Docetaxel(every 3 weekly)+Prednisone	TAX327 [24]	Mitoxantrone+Prednisone	0.76	18.9Vs 16.5	0.009
Cabazitaxel(post docetaxel)	TROPIC [26]	Mitoxantrone+Prednisone	0.70	15.1 vs 12.7	<0.0001
Sipuleucel-T	IMPACT [11]	Palcebo	0.78	25.8Vs 21.7	0.03
Abiraterone+ADT +prednisone	STAMPEDE [14]	ADT	0.60	NRP(5 year survival 60% Vs 41%)	NRP
Abiraterone+ADT +prednisone	LATITUDE [15]	ADT+Placebo	0.62	NRP	<0.001
Docetaxel	CHAARTED [25]	ADT	0.61	57.6 Vs 44	<0.001

OS: Overall Survival; MFS: Metastases Free Survival; NRP: Not reported.

Ethical policy

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study. Approval from institutional ethical committee was taken.

Availability of data and materials

All data generated or analysed during this study are included in this publication.

Author contributions

Dr. Nishant Lohia carried out review of various articles and texts and them compiling, proof reading, editing and final drafting of manuscript.

Competing interests

None identified.

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