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Review Article

Medical Management of Castration Resistant Prostate Cancer (CRPC): Beyond Chemotherapy

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Abstract

Prostate cancer is one of the leading causes of cancer-related mortality in men. Despite advances in treatment options, about 30-40% of patients develop the advanced disease in due course. Androgen deprivation is the standard first-line systemic therapy for men with advanced prostate cancer. Almost all patients with the metastatic disease go on to develop castration-resistant prostate cancer. The multiple therapeutic alternatives for castration-resistant prostate cancer, including abiraterone acetate, enzalutamide, cabazitaxel, immunotherapy with sipuleucel-T, radiopharmaceuticals and bone-targeted therapies (zoledronic acid, denosumab) along with docetaxel have made the decision-making process complex and challenging for clinicians. Even the strong pipeline of systemic therapies with a diverse array of mechanisms of action in prostate cancer have shown preliminary signs of clinical benefit, leading to more definitive phase III confirmatory trials. The review will relate the pathogenesis to the management of castration-resistant prostate cancer and look for the best therapy approaches in metastatic castration-resistant prostate cancer, needed to tackle the existing challenges effectively.

Keywords: Castration Resistant Prostate Cancer; Prostate Cancer; AR signaling inhibitor; metastatic; asymptomatic

Abbreviation: GLOBOCAN: Global Cancer Incidence, Mortality and Prevalence; CRPC: castration-resistant prostate cancer; mPC: metastatic prostate cancer; mCRPC: metastatic castration-resistant prostate cancer; NM-CRPC: non-metastatic CRPC; FDA: Food and Drug Administration; PSA: prostate-specific antigen; EAU: European Association of Urology; AA: abiraterone acetate; RECIST: Response Evaluation Criteria in Solid Tumors; ADT: androgen deprivation therapy; LBD: ligand binding domain; MAPK : mitogen-activated protein kinases; BRCA: breast cancer gene; ATM: ataxia telangiectasia mutated; AUA: American Urological Association; NEPC: Neuroendocrine prostate cancer

Introduction

Prostate cancer, with an estimated 1.4 million new cases and over 381,000 deaths annually, is a common cancer among men. It has the highest incidence among all cancers in 92 countries [1].

Prostate cancer

Incidence and mortality rates in South Central Asia were reported to be 5.0 and 3.3 per 100,000 person-years, respectively, as per Global Cancer Incidence, Mortality and Prevalence

(GLOBOCAN) 2018 [2]. Approximately, 10 to 20% of newly diagnosed patients present with metastatic disease [3]. Almost all patients with metastatic prostate cancer (mPC) go on to develop castration-resistant prostate cancer (CRPC) [4]. A hospital-based survival study from Mumbai, India reported approximately 71% patients had mPC at diagnosis while another population based study reported that non-metastatic CRPC (NM-CRPC) represents only 3% of total PC population in Asian countries (China, India, Japan, Russia, and Turkey) [5,6]. Overall prognosis of metastatic castration-resistant prostate cancer (mCRPC) remains poor with a median survival of 1–2 years. Until recently, treatment options for mCRPC patients have been limited to docetaxel-based regimens [7,8]. Although docetaxel is associated with modest survival benefit, the availability of new frontline treatment regimens including sipuleucel-T, cabazitaxel, abiraterone acetate (AA) and enzalutamide, reporting longer survival, have extended the treatment options for men with mCRPC [9-11]. Recent phase III trials, SPARTAN, PROSPER and ARAMIS have demonstrated efficacy of the apalutamide, enzalutamide and darolutamide, respectively in NM-CRPC, a condition which has historically lacked level 1 evidence for treatment [12,13]. Thus, these Food and Drug Administration (FDA) approved new drugs can now be offered to the patients with NM-CRPC [14,15]. Selecting the correct treatment for mCRPC is complex as no head-to-head trials have been conducted and comparison between existing trials is difficult due to differences in study populations and lack of validated biomarkers. Multiple factors like treatment sequence, symptom burden, metastasis type, comorbidities and patient preference are taken into consideration for treatment decisions [16]. While new treatment paradigms are emerging and guidelines continue to evolve for management of patients with CRPC across the world, there is no standard of care in India. This review will relate the pathogenesis to management of CRPC and look for the best therapy approaches in mCRPC needed to tackle the existing challenges effectively.

Defining CRPC: guideline perspective

Several professional associations have developed guidelines for prostate cancer and have defined CRPC based on clinico-pathologic, radiographic or biochemical progression (Table1) [17-21]. The European Association of Urology (EAU) has standardized CRPC diagnosis based on four defining factors; castrate levels of serum testosterone (<1.7 nmol/L), 3 consecutive increases in prostate-specific antigen (PSA) one week apart resulting in two 50% increases above the nadir, a PSA >2 ng/mL and appearance of either two or more new bone lesions observed with bone scan or a soft tissue lesion using RECIST (Response Evaluation Criteria in Solid Tumors). It also recommends investigation of symptomatic progression alone though it is not sufficient to diagnose CRPC [18]. NM-CRPC refers to a rising PSA level under androgen deprivation therapy (ADT) with a castration level of testosterone and no clinically detectable metastatic disease while mCRPC is characterized by disease progression following surgical or medical castration in the presence of clinically detectable metastatic disease [18,22].

Table 1: CRPC Definition as per Guidelines.

Organization	CRPC Definition	Ref
NCCN guidelines	"CRPC is prostate cancer that progresses clinically, radio graphically or biochemically despite castrate levels of serum testosterone (<50 ng/dl)	[17]
EAU/ESTRO/SIOG	Castrate serum testosterone <50 ng/dl or 1.7 nmol/l plus one of the following types of progression: i) Biochemical progression: >2ng/mL higher than the nadir. 3 consecutive rises in PSA one week apart, resulting in two 50% increases over the nadir ii) Radiologic progression: The appearance of new bone lesions: either two or more new bone lesions on bone scan or a soft tissue | lesion using the RECIST criteria	[18]
AUA	Patient with a rising PSA despite medical or surgical castration (serum testosterone <50 ng/dl) with or without: 1. Radiologic evidence of mPC 2. Prior Docetaxel therapy Rising PSA: >2ng/mL higher than the nadir; the rise has to be at least 25% over nadir and	[19]

CRPC= Castration- resistant prostate cancer, RECIST= Response evaluation criteria in solid tumors, NCCN= National Comprehensive Cancer Network, PSA= Prostate-specific antigen, M0= Non metastatic, EAU/ESTRO/SIOG= European Association of Urology/ European Society for Radiotherapy and Oncology/ International Society of Geriatric Oncology, AUA= American Urology Association, CUA= Canadian Urological Association, ESMO= European Society for Medical Oncology, mPC= metastatic prostate cancer.

Events in the course of prostate cancer progression to castration-resistant prostate cancer

The mechanisms and timing of development of CRPC are unclear and remain debatable. After the initial response to ADT, most of the patients with prostate cancer eventually develop the castration-resistant state. Approximately 33% of men with CRPC go on to develop metastases within 2 years of CRPC diagnosis. Various analyses indicate that progression to CRPC is multifactorial [23]. The "adaptation" model and the "clonal selection" model are two mechanisms that have been proposed to address this question. The adaptation model suggests that primary prostate cancer cells are homogeneous, in terms of their androgen requirement, and castration-resistant state emerges through genetic/epigenetic conversion of androgen-dependent cells to androgen-independent

cells while the clonal selection model proposes that primary prostate cancer cells are heterogeneous with regards to their androgen requirement, of which a minority is a clone of pre-existing castration-resistant cells [23]. The progression of tumor growth and development of metastases despite reduction of serum androgens to 'castrate' levels is dependent upon the utilization of adaptive cell-survival pathways. Mechanisms contributing to CRPC and its progression include various androgen/androgen receptor dependent and independent pathways (Figure1).

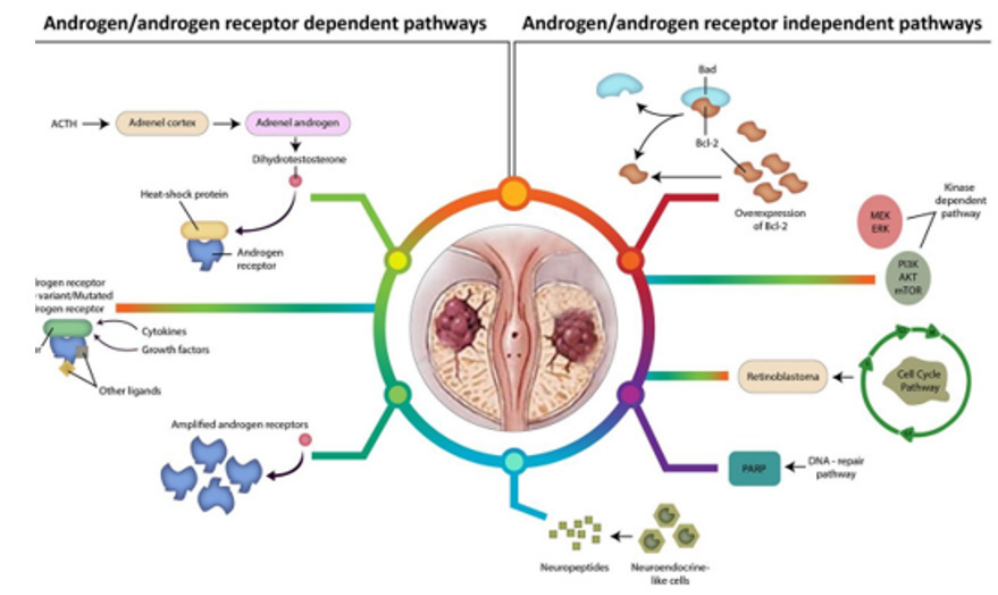

Figure 1: Mechanisms contributing to CRPC progression.

ACTH- Adrenocorticotropic hormone, PARP- polyADP-ribose polymerases, PI3K - phosphatidylinositol 3-kinase, Akt -Protein Kinase B, Bcl-2 -Antiapoptotic protein, Bad - BH3 proteins Sensitizer , mTOR-mammalian target of rapamycin, MAPK/ERK- mitogen- activated protein kinases.

Androgen/androgen receptor dependent pathway

Intraprostatic steroidogenesis: Studies have suggested that testosterone levels in prostate of men with CRPC are equivalent of those found in non-castrate patients. Up regulation of enzymes involved in androgen synthesis in prostate cancer cells is hypothesized to be the underlying mechanism of increased testosterone in prostate of CRPC patients [24].

Increased sensitivity of androgen receptor (AR): In CRPC patients, activation of the AR signaling pathways occurs through the genetic phenomena that result in increased sensitivity of AR to very low levels of androgens [24,25].

AR mutations: Mutations of the AR gene have been found in 10% to 30% of CRPC patients. These mutations lead to changes in ARs that affect the ligand binding, reduce specificity and increase promiscuity of binding to non-androgen ligands [24].

AR splice variants: The majority of AR splice variants (AR-Vs) identified to date in prostate cancer cells are generated through insertion of downstream cryptic exon or deletions within the ligand binding domain (LBD), producing truncated AR lacking LBD, rendering them impervious to commonly utilized anti-androgen agents [26,27].

Androgen/androgen receptor independent pathway

Altered apoptotic pathway: In particular, B-cell lymphoma-extra-large (Bcl-xL) expression increases during prostate cancer progression from primary to castration-resistant state. Activated ligand-independent AR signaling has been found to be associated with increased levels of Bcl-xL [28].

Kinase-dependent pathway: Deregulation of the kinase-dependent signaling pathways, MAPK/ERK (mitogen-activated protein kinases) or PI3K-AKT-mTOR (phosphoinositide-3-kinase-AKT-mammalian target of rapamycin), has been found to be associated with mCRPC in >50% of patients. These pathways are involved in a variety of biological processes such as cell survival, proliferation, differentiation, apoptosis, survival, invasion, and migration as well as angiogenesis [29].

Alteration in DNA repair pathway: Deleterious germ line or somatic aberrations in DNA damage repair genes have been found in 19% and 23% of primary prostate cancer and mCRPC respectively, with breast cancer gene (BRCA), cyclin-dependent kinase 12 (CDK12) & ataxia telangiectasia mutated (ATM) as the commonly altered gene [29].

Alteration in cell cycle pathway: Retinoblastoma (RB) gene product is a critical inhibitor of transition from G1–S phase, preventing premature cell division [30]. RB gene loss is reported in 21% of CRPCs and its inactivation promotes the reprogramming of differentiated cells to a pluripotent state [29].

Treatment-related neuroendocrine prostate cancer: Neuroendocrine prostate cancer (NEPC) is a subtype of prostate cancer that rarely arises de novo, but commonly arises after hormonal therapy [31]. It also has aggressive biologic behavior and poor outcomes

Management of CRPC

The treatment of prostate cancer has been rapidly changing and is still evolving. Despite a high initial response rate (80-90%) with ADT, nearly all patients with prostate cancer eventually develop progressive disease. Persistent AR signaling is an important driving force for their progression and thus, AR signaling axis represents the most important therapeutic target for the treatment of both castration naïve prostate cancer and CRPC. In castration-naïve prostate cancer, patients with biochemical recurrence should be risk stratified based on the Gleason score, time to biochemical recurrence and PSA doubling time. Evidence suggests that only high-risk biochemical recurrence patients should be considered for ADT. In addition, current practice supports the use of ADT in the setting of metastatic hormone naïve prostate cancer [32].

Therapy of men with non-metastatic castration-resistant prostate cancer: After almost 20 years of negative outcomes in clinical trials involving men with NM-CRPC, AR antagonists namely apalutamide, enzalutamide and darolutamide have shown favorable outcomes in three different trials (SPARTAN, PROSPER, ARAMIS trials) [3,12]. Based on results of these trials, US FDA has approved these drugs (apalutamide, enzalutamide and darolutamide) for the treatment of NM-CRPC. In the SPARTAN trial, 1,207 men with NM-CRPC at high risk of disease progression were randomized in a 2:1 fashion to receive either apalutamide 240 mg orally daily with ADT (n =806) or placebo with ADT (n=401) [12]. The median metastasis-free survival (MFS) for patients treated with apalutamide was 40.5 months versus 16.2 months for the placebo arm (HR 0.28, 95% CI 0.23–0.35; P<0.001). Apalutamide also reduced the risk of symptomatic progression by 55% (HR 0.45, 95% CI: 0.32–0.63; P<0.001). Estimated rates of any adverse events (AEs) that led to discontinuation of the trial regimen were 10.6% for apalutamide and 7.0% for placebo, respectively. Apalutamide-treated patients had a higher incidence of rash (23.8% vs. 5.5%), fracture (11.7% vs. 6.5%) and hypothyroidism (8.1% vs. 2.0%) than with placebo. In another randomized phase III PROSPER trial, a total of 1,401 men with NM-CRPC were randomized in a 2:1 fashion to receive enzalutamide 160 mg or placebo once daily [13]. Enzalutamide significantly increased MFS (36.6 months vs. 14.7 months; HR 0.29; P < .0001), time to PSA progression (37.2 months vs. 3.9 months; HR 0.07; P < .0001) and time to first use of new antineoplastic therapy (39.6 months vs. 17.7 months; HR 0.21; P < .0001) compared to placebo [13]. The estimated rates of any AEs leading to discontinuation were 10% for enzalutamide and 8% for placebo. The overall incidence of AEs was higher with enzalutamide than with placebo (any grade: 87% vs. 77%; grade ⩾3: 31% vs. 23%; serious: 24% vs. 18%) [13].

In 2019, the results of double-blind, placebo-controlled, phase III ARAMIS trial evaluating darolutamide for the treatment of advanced prostate cancer were published [33]. A total of 1509 patients with NM-CRPC were randomized in a ratio of 2:1 to receive darolutamide 600 mg (two 300 mg tablets) twice-daily or placebo, while continuing androgen deprivation therapy. Darolutamide significantly increased MFS (40.4 months vs. 18.4 months; HR 0.41; 95% CI 0.34–0.50; P< .0001), overall survival (HR 0.71, 95% CI 0.50–0.99; 2-sided p=0.045), and time to pain progression (HR 0.65; 95% CI 0.53–0.79; 2-sided p<0.0001) compared to placebo. The estimated rates of any AEs leading to discontinuation were 8.9% for darolutamide and 8.7% for placebo. The incidence rate of treatment-emergent AEs were also comparable between darolutamide and placebo arms (≥5% frequency for grade ⩾3 AEs). American Urological Association (AUA) guidelines 2018 on prostate cancer have recommended use of apalutamide or enzalutamide in patients with NM-CRPC at high risk for developing metastatic disease, along with continued androgen deprivation. Those patients who do not want or cannot have one of the standard therapies should either be under observation with continued androgen deprivation or may be offered treatment with a second-generation androgen synthesis inhibitor (i.e. AA + prednisone), if at high risk for developing metastatic disease. Although similar in mechanism, darolutamide does not cross the blood-brain barrier and thus confers a much lower seizure risk than enzalutamide or apalutamide [19].

Therapy of men with metastatic castration-resistant prostate cancer: Currently, the guidelines from AUA and National Comprehensive Cancer Network (NCCN) recommend FDA-approved therapies in mCRPC patients to improve survival and palliate symptoms. Treatment options include sipuleucel-T, docetaxel-based chemotherapy and novel hormonal therapies [such as enzalutamide and AA plus prednisone (AAP) [17,19,34]. If patients fail on these therapies, alternative treatment options include radiopharmaceutical therapy (radium-223 dichloride) and cabazitaxel [34]. Both taxane-based chemotherapy and AA require concomitant use of corticosteroids [8,35]. Guidelines from the AUA, EAU and NCCN recommend prednisolone while current clinical trials suggest dexamethasone may be more potent compared to prednisolone in the treatment of mCRPC [17-19,36-38]. The NCCN 2019 recommends sipuleucel-T for asymptomatic patients with mCRPC having Eastern Cooperative Oncology Group performance status of 0–1 and have life expectancy of more than six months [17]. In addition, pembrolizumab may also be offered to patients who have progressed following at least one systemic therapy for M1 CRPC (presence of metastases) [17].

Newer anti-androgens, like enzalutamide and AA, were developed to overcome the efficacy limitation of first-generation anti-androgens in the setting of AR over-expression or of specific mutations in the AR ligand-binding domain. Enzalutamide has five-to-eight times higher binding affinity for AR than bicalutamide;

it inhibits AR nuclear translocation and impairs binding of AR to androgen response elements on DNA and their activation [39]. Enzalutamide is also active against prostate cancer cell lines bearing the W741C AR point mutation that is known to confer resistance to bicalutamide [40]. It has shown encouraging activity both among chemotherapy-experienced and chemotherapy-naive mCRPC patients [41], although a clinical study demonstrated that proportion of patients achieving PSA decline in excess of 50% with enzalutamide is higher among the chemotherapy naïve patients (57%; 95% CI 44-69%) than in chemotherapy experienced patients (36%; 95% CI 25-48%) at 12 weeks [42].

A network meta-analysis of eight randomized controlled trials was conducted by Kang et al. to compare the efficacy of novel AR-targeted agents in patients with mCRPC (5 studies in the pre-chemotherapy and 3 in the post-chemotherapy settings) [43]. This meta-analysis found significantly improved overall survival (OS) with enzalutamide and AA as compared to control arms. Network meta-analysis also showed that enzalutamide ranked first as the most efficacious agent in improving OS (HR = 0.71) and AA was ranked second in this regard (HR=0.78). Further, enzalutamide significantly improved progression-free survival (PFS) in comparison with control groups (HR = 0.36), and a trend towards improved PFS was observed with AA. In comparison to control groups, Enzalutamide (HR = 0.20) and AA (HR=0.56) were significantly associated with prolonged times to PSA progression.

Treatment of chemotherapy exposed mCRPC patients: In 2017, Rocha et al. conducted a retrospective cohort study to investigate the impact of AA with and without prior docetaxel chemotherapy on the survival of patients with mCRPC using Quebec public health care administrative databases [44]. The median age at initiation of AA therapy was 75 years for the post-docetaxel-chemotherapy group and 80 years for the other patient group, without chemotherapy. The median survival in the two groups was 12 and 14 months (log-rank test p = 0.8), respectively. Risk of death was similar in the 2 groups (adjusted HR 0.89 [95% CI 0.57-1.38]). This study showed that effectiveness of AA in older patients who were ineligible for chemotherapy was similar to that of patients with prior docetaxel exposure. Overall, the real-world survival benefits of AA were similar to those in the COU-AA-301 trial. Similarly, in AFFIRM study, median OS was 18.4 months with enzalutamide (n = 800) versus 13.6 months in the placebo arm (n = 399) in patients of mCRPC who had relapsed following docetaxel-based chemotherapy (HR for death in the enzalutamide arm, 0.63; 95% CI, 0.53 to 0.75; P<0.001) [10]. In each study group, about 92% of men had bone metastases at baseline. Compared with placebo, enzalutamide reduced the risk of death by 33% (HR 0.67; 95% CI, 0.52–0.87) in those with >20 and 41% (HR 0.59; 95% CI, 0.46–0.75) in those with ≤20 bone lesions, respectively. Enzalutamide was also superior to placebo for time to first reportable skeletal-related event (SRE) (16.7 vs. 13.3 months, respectively; HR 0.69; 95% CI, 0.57– 0.84; P < 0.001). Data from STRIVE trial has demonstrated the superiority of enzalutamide over bicalutamide in patients with or without metastatic CRPC (n=396) who progressed despite ADT. Enzalutamide reduced the risk of progression or death by 76% versus bicalutamide (HR 0.24; 95% CI, 0.18 to 0.32; P < .001) [45]. Median time to PSA progression (HR 0.19; P < 0.001) and PFS (median PFS duration: 16.5 vs. 5.5 months; HR 0.24, P < 0.001) were significantly improved with enzalutamide as compared to bicalutamide. The side effects were comparable between groups; grade ≥3 AEs and treatment-related deaths occurred in 36% of patients and in 3% of patients in each group, respectively.

Radium-223 (Ra-223) is an alpha particle emitter and calcium-mimetic that is used for therapy of patients with CRPC having symptomatic bone metastasis. Ra-223 delivers high energy but short-range radiation, limiting damage to normal tissues [46]. Ra-223 improves OS and delays time to first symptomatic skeletal-related events in mCRPC patients [47]. In phase I/IIa clinical trial, Ra-223 plus docetaxel combination, in comparison to docetaxel alone, prolonged time to progression of PSA (median time to progression, 6.6 vs. 4.8 months), improved PFS (median PFS 12.0 months vs. 9.3 months) and prolonged time to progression of total alkaline phosphatase (ALP) and bone ALP (9.0 vs. 6.9 and 9.3 vs. 7.4 months, respectively) [48].

Treatment of chemotherapy naive mCRPC patients: Enzalutamide and AA with prednisone have also received the highest recommendation (category1) in the NCCN guidelines for the first line therapy of patients with asymptomatic, chemotherapy naive mCRPC [17]. Cluster ranking of one of the meta-analysis involving 18 studies in pre-chemotherapy settings demonstrated that enzalutamide and AA were ideal agents for improving PFS and OS in chemotherapy-naïve mCRPC patients with a low risk of causing severe AEs [49]. In double-blind, phase 3 PREVAIL trial, the risk of radiographic progression (81% risk reduction; HR 0.19; 95% CI, 0.15 to 0.23; P<0.001) and death (29% reduction in the risk of death; HR 0.71; 95% CI, 0.60 to 0.84; P<0.001) were significantly reduced by enzalutamide vs. placebo in patients with chemotherapy naive mCRPC. Enzalutamide also delayed the initiation of chemotherapy in these patients [50]. The results from long-term overall survival and safety analyses of the phase 3 PREVAIL study showed significant OS benefit with 32.4 months in the enzalutamide arm vs. 30.2 months in the placebo arm at the median follow up time of 69 months. In overall survival analysis, enzalutamide resulted in 17% reduction in the risk of death (HR 0.83, 95% CI 0.75-0.93, p=0.008) [51]. Similarly, in the COU-AA-302 phase 3 trial, overall survival for men with chemotherapy-naive mCRPC was significantly longer in the AA plus prednisone (n = 542) than in the prednisone alone (n = 546) group (34·7 months [95% CI 32·7–36·8] vs. 30·3 months [95% CI 28·7–33·3]; HR 0·81 [95% CI 0·70–0·93]; p=0·0033) [52].

Treatment of asymptomatic or minimally symptomatic mCRPC patients: The autologous, active cellular immunotherapy, sipuleucel-T which utilizes patient's own antigen-presenting cells, is an FDA approved agent for therapy of asymptomatic or minimally symptomatic mCRPC [17]. Randomized Phase III trial (D9901) evaluating the effect of sipuleucel-T in men with asymptomatic mCRPC has shown improvement in mean survival from 21.4 months to 25.9 months. Study result revealed that the safety profile

of sipuleucel-T was similar to that of placebo [53]. In D9902A trial, sipuleucel-T showed non-significant 21% reduction in risk of death compared to placebo among men with asymptomatic mCRPC (HR 1.27; 95%CI, 0.78-2.07; P = .33). Additionally, when data from the D9901 and D9902A trials were integrated, significant increase in median OS for the sipuleucel-T group versus placebo was observed with a benefit of 4.3 months (HR 1.50; 95% CI 1.10–2.05; log rank p = 0.01) [54]. In 2016, a randomized, double-blind, phase 2 TERRAIN trial compared enzalutamide to bicalutamide in patients with asymptomatic/mildly symptomatic mCRPC who progressed despite ADT. Enzalutamide significantly increased the median progression-free survival (15·7 months [95% CI, 11·5-19·4]) versus bicalutamide (5·8 months [95% CI, 4·8-8·1]; hazard ratio 0·44 [95% CI 0·34-0·57]; p<0·0001). Median follow-up time was also longer for the patients treated with enzalutamide group (20 months) compared with 16.7 months in the bicalutamide group [55].

Selecting appropriate therapies in the mCRPC patient

As CRPC progresses to advanced stage (i.e. mCRPC), a multidisciplinary approach is needed to improve survival and quality of life of the patients. At the same time, little is known about optimal sequencing and combination strategies, and how cross resistance can evolve for subsequent treatments [56]. Front line therapies include docetaxel, sipuleucel-T, AA/prednisone, enzalutamide and Ra-223. The AUA guidelines consider different scenarios based on chemotherapy naïve or exposed mCRPC patients [19].

Chemo-naïve patients having:

a) Asymptomatic or minimally symptomatic mCRPC- may receive AAP, enzalutamide, or docetaxel chemotherapy and sipuleucel-T immunotherapy

b) Symptomatic mCRPC and good performance status- may receive AAP, enzalutamide, or docetaxel

c) Symptomatic mCRPC, poor performance status- may receive AAP or enzalutamide.

Chemo-exposed with docetaxel:

a) Symptomatic mCRPC, good performance status- may receive AAP, cabazitaxel, or enzalutamide

b) Symptomatic mCRPC, poor performance status- should not be offered AAP

However, grade A evidence is lacking for combinations or sequential use of the above-mentioned therapies, apart from the use of Ra-223 after docetaxel, leaving clinicians with imperfect guidance on treatment selection for individual patients [57]. Despite limitations, some consistent observations have arisen from studies. First, cross-resistance occurs between the new androgen-receptor–targeting agents. The rate of response to AA therapy after treatment with enzalutamide is less than 10%, whereas the response rate for enzalutamide after AA is 15 to 30% [58-60]. However, major progress can be expected by the validation of predictive biomarkers of cross-resistance between these treatments and might lead to more rational sequencing strategies with more accurate patient selection. Although cross-resistance between the two agents have been observed in a majority of patients, but some still get benefit from enzalutamide treatment following ≥24 week of AA plus prednisone treatment [61]. The benefit from taxanes appears to be diminished after treatment with AA or enzalutamide, as compared with the benefit in patients who have not received such treatment, although taxanes remain active [62]. Guidance in treatment decisions for such patients is limited as large, prospective, randomized trials with taxanes in men having already treated with AA or enzalutamide, are not available. Potential synergistic activity between agents has led to the evaluation of multiple combinations. No combination has been proven to have superior efficacy in mCRPC to date; nine randomized phase 3 trials enrolling more than 10 000 patients failed to prove the benefit of any docetaxel combination. The phase III ALpharadin in SYMPtomatic Prostate CAncer (ALSYMPCA) trial has reported that Ra-223 should be considered as a treatment option for patients with CRPC and symptomatic bone metastases. Owing to low toxicity rates of Ra-223 observed in ALSYMPCA and non-overlapping mechanism of action, its combinations with AA or enzalutamide, have attracted interest. In an expanded access program (EAP) from USA, no new safety concerns were reported with Ra-223; safety was maintained with AA or enzalutamide [63, 64]. The ongoing PEACE-3 trial is now evaluating the combination of enzalutamide and Ra-223 in mildly symptomatic mCRPC (EUDRACT 2014-001787-36). However, it is not a foregone conclusion that any of these combinations will improve outcome. In a neoadjuvant study of 24 weeks, the combination of enzalutamide, AA, and leuprolide acetate showed pathologic down staging in only 30% of patients relative to 52% of patients receiving AA and leuprolide acetate, calling into question the synergy between these novel hormonal agents [65].

The Post-Abiraterone /Post-Enzalutamide Space

The question of what to do with patients with mCRPC who had failed treatment with AA is currently subject to debate. Since 2004, docetaxel has been viewed as standard of care for chemotherapy naïve mCRPC patients, but results are mixed at best. The de Bono group has reported diminished response to docetaxel in patients who have already received AA treatment [66]. There are no large trials in this setting so conclusions must be tempered until more data are available. Fizazi and colleagues have reported relatively high PSA response rates for cabazitaxel/prednisone in patients previously treated with AA [67]. However, there is need to learn about characteristics of the treated patients and response durability as this study was only published in abstract form.

In 2014, a study by Schrader et al. [59] indicated that the response to enzalutamide post-AA/post-docetaxel was only modest compared to the patients treated post-docetaxel alone [60]. However, one study by Schler et al. have reported positive results for enzalutamide in patients previously treated with docetaxel. In this study, 56% of men achieved a >50% decline in PSA and only 17% had no PSA response [68]. Thomson and colleagues have also reported enzalutamide activity following failure of docetaxel and AA in mCRPC. This activity was more pronounced in those who have responded to AA [69].

Newer Treatments in Managing CRPC

The current treatment strategies are still less than satisfactory and have paved way for the novel agents in effectively treating CRPC. A considerable number of novel agents against mCRPC based on diverse mechanisms are currently under investigation worldwide (Table2). A number of novel agents (buparlisib, ipataserib, olaparib, palbocicilib etc) that act against mCRPC based on diverse mechanism (PI3K-AKT-mTOR pathway inhibitor, PARP inhibitor and CDK inhibitor) are currently under investigation worldwide. List of newer treatments along with their mechanism of action are shown in the Table 2 [70-82].

Table 2: Newer treatments for CRPC

Treatment Pathways	Agents	Mechanisms	Outcomes
CDK inhibitor [70]	Ribociclib	CDK4/6-specific inhibition	Currently in phase 1 and 2 trials
AURKA inhibitor [70]	Alisertib	Aurora A kinase inhibitor	Currently in phase 1 and 2 trials
Therapeutic vaccines [70]	DC-VAC	Autologous immunotherapy	Currently in Phase III trials for mCRPC
Cytokines inhibitor [70]	CY107	-	Currently in Phase II trial for mCRPC patients with sipleucel-T
PI3K-AKT-mTOR pathway inhibitor [71, 72]	Buparlisib	Pan PI3K inhibitor	Did not improve PFS in men with mCRPC progressing on enzalutamide
	Ipatasertib	AKT inhibitor	In mCRPC, combined blockade with AA and ipatasertib showed superior antitumor activity to AA alone, especially in patients with PTEN-loss tumors.
Ras-Raf-MEK-ERK pathway inhibitor [73]	Sorafenib	Raf inhibitor 32	Pharmacologic targeting of the MEK/ERK pathway may be a viable treatment strategy for patients with refractory metastatic prostate cancer.
	Trametinib	MEK 1/2 inhibitor	Trametinib elicited a profound biochemical and clinical response in a patient who had failed multiple prior treatments for mCRPC.
PSMA ligands [74, 75]	Lutetium-177	PSMA over-expression led to the use of PSMA ligands for CRPC	PSMA-avid metastases of prostate cancer
	Galliuum-68		PSMA-avid metastases of prostate cancer
Checkpoint inhibitors [76]	Atezolizumab	PD-L1 inhibitor	Currently in Phase III trial for mCRPC patients with enzalutamide
	Durvalumab	PD-L1 inhibitor	Currently in Phase II trial for mCRPC
	Tremelimumab & Ipilimumab	CTLA-4 inhibitors	Currently in phase II and phase III trials for mCRPC
Quinolone-3-carboxamide [77]	Tasquinomod	Immunomodulator compound	Currently in phase III trial for mCRPC
Clusterin	Custirsen	Protective, anti-33	Currently in phase III trial for
inhibitor [78]		Apoptotic chaperone protein	mCRPC patients with cabazitaxel/ prednisone
Oncolytic[[70,79,80]	Talimogenelaherparepvec, Reolysin, ProstAtek	Tumor-selective, multimechanistic antitumor agents	Oncolytic virus therapy for prostate cancer

ADC [80]	Tisotumab vedotin	Tissue Factor specific human IgG1 monoclonal antibody conjugated to a microtubule disrupting agent Monomethyl Auristatin E	Currently, it is under phase II trial in Patients with solid tumors
PARP inhibitor [70, 81, 82]	Olaparib	DNA repair pathway blocker	Efficacious and well tolerated in patients with mCRPC
	Veliparib		High efficacious in mCRPC with erythroblast transformation-specific fusion positive tumors in a phase II study
	Niraparib Rucaparib		Currently in phase II and III trials

Conclusion

The management of advanced prostate cancer has undergone a revolution over the last decade with the emergence of new science and evidences in novel bone-targeted agents, immunotherapy, chemotherapy and AR pathway-targeted agents. In clinical trials, AA, enzalutamide, and Ra-223 improved the radiographic progression-free survival and overall survival in patients with mCRPC compared with placebo. Overall, enzalutamide was found to be most effective treatment option for mCRPC patients in both chemotherapy naïve and pre-treated setting. In addition to enzalutamide, Grade A evidence also supports the use of sipuleucel-T, AA–prednisone, docetaxel, and Ra-223 in chemotherapy naïve setting while in pre-treated patients, use of AA–prednisone, cabazitaxel, and Ra-223 has been supported. However, Grade A evidence is lacking for combination or for sequential use of these therapies, apart from the use of Ra-223 after docetaxel. Prospective randomized clinical trials addressing the best therapy approaches in mCRPC are required to determine evidence-based sequencing strategies.

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