An Integrative Approach for Sequencing Therapies in Metastatic Prostate Cancer

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Abstract

Prostate cancer is the most commonly diagnosed cancer in American men, and metastatic castration-resistant prostate cancer (mCRPC) was responsible for an estimated 26,120 US deaths in 2016. Over the past decade, 6 agents have been approved by the FDA for mCRPC, which fall into the broad categories of androgen-directed therapies, immunotherapy, chemotherapy, and bone-targeting agents. A lack of consensus currently exists on optimal sequencing of these therapies in mCRPC. In routine clinical practice, the patient's treatment history and medical comorbidities play a critical role in tailoring management. At centers with infrastructural capacity to generate and administer personalized vaccines, sipuleucel-T can be used as first-line treatment in asymptomatic patients, but robust predictive biomarkers are lacking. More commonly, abiraterone or enzalutamide are used as first-line and second-line treatments for asymptomatic or symptomatic patients, followed by docetaxel and cabazitaxel as third- and fourth-line treatments, respectively. Radium-223 can be used to alleviate pain associated with bone metastases, regardless of prior chemotherapy status. A paucity of data exists regarding optimal therapy for patients with mCRPC who have progressed on androgen-directed therapy and chemotherapy, at which point genomic sequencing and enrollment into clinical trials is the way forward. Several ongoing clinical trials with PARP inhibitors are showing considerable promise, and they will likely result in the development of novel combination strategies to treat mCRPC.

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Introduction

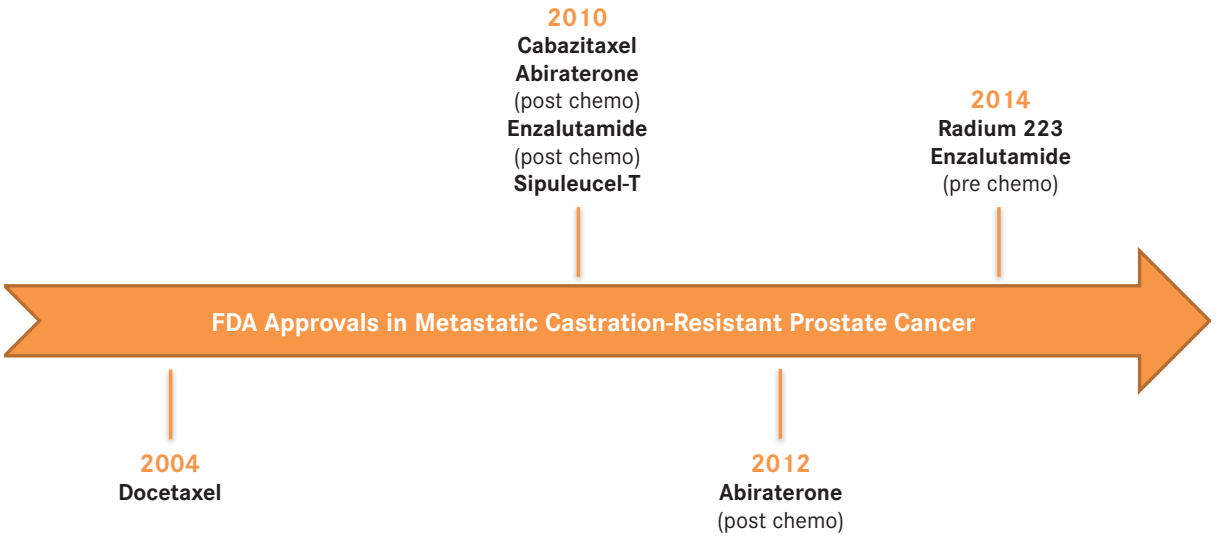
Prostate cancer is the most common cancer and the second leading cause of cancer-related death among men in the United States.[1] The majority of patients with prostate cancer present with localized disease at the time of diagnosis.[2] However, metastatic castration-resistant prostate cancer (mCRPC) was responsible for an estimated 26,120 US deaths in 2016.[3] The current standard of care for patients with metastatic prostate cancer is androgen-deprivation therapy (ADT). Most patients initially respond well to ADT in the form of surgical or chemical castration, which lasts for a median duration of 18 months to 2 years, following which the disease becomes castration resistant.

With a multitude of FDA-approved treatment options for mCRPC, which include abiraterone acetate (Zytiga), enzalutamide (Xtandi), docetaxel (Taxotere), cabazitaxel (Jetvana), sipuleucel-T (Provenge), denosumab (Xgeva), and radium-223 (Xofigo), the optimal treatment sequence for these therapies remains a conundrum in the field. In addition, there are limited data to guide sequencing of later lines of therapy and the utility of combining existing therapies. Given the recent practice-changing data demonstrating a significant overall survival (OS) improvement with docetaxel and abiraterone use in frontline therapy for hormone-sensitive, locally advanced, and metastatic prostate cancer, the future of these agents following mCRPC progression remains to be determined.[4,5] The main objective of this article is to provide a comprehensive, evidence-based review of the selection and sequencing of different lines of therapy for mCRPC.

Current Landscape

Although several new agents have become available to treat mCRPC in the past decade (**Figure 1**), limited evidence provides guidance for sequencing these treatments in routine clinical practice. In 2004, the chemotherapeutic agent docetaxel became the first agent to receive

FIGURE 1. Several New Agents Approved Since 2004



FDA approval in mCRPC.[6] This approval was based on 2 clinical trials, TAX 327 and SWOG 99-16.[6] Both studies showed that docetaxel improved median survival relative to mitoxantrone.[7,8] Cabazitaxel is another taxane-based chemotherapy that was approved by the FDA, in 2010, in patients with mCRPC previously treated with docetaxel.[9] Both docetaxel and cabazitaxel work by disrupting cellular microtubule dynamics that are critical for mitosis and cell division.[10] Study findings suggest that cabazitaxel has a better pharmacokinetic profile than docetaxel, but the former is more myelosuppressive, resulting in a higher incidence of febrile neutropenia.[11,12]

In the FIRSTANA trial,[13] which studied cabazitaxel versus docetaxel as first-line therapy in chemotherapy-naïve mCRPC, different dosages of cabazitaxel did not show superiority over docetaxel, with each agent having different toxicity profiles but overall less toxicity with lower-dose cabazitaxel. Cabazitaxel is used mostly in cases of progression on docetaxel since it was designed to overcome the resistance mechanisms to docetaxel, and this remains the only indication for which it is FDA approved. Given their potential toxicities and the established efficacy of less toxic alternatives, such as androgen-directed therapies (see below), taxane-based chemotherapy agents are generally reserved for use as second- or third-line therapies.[14]

From 2011 to 2012, 2 androgen-directed therapies, abiraterone acetate and enzalutamide, were approved by the FDA for patients with mCRPC, initially in the postchemotherapy setting.[15] Abiraterone inhibits testosterone production in the adrenal glands, testes, and prostate via inhibition of CYP17A1.[16] Enzalutamide antagonizes the androgen receptor (AR) with higher binding affinity relative to prior AR antagonists, such as flutamide, nilutamide, and bicalutamide.[16]

The approval of abiraterone was based on a multinational phase III trial, COU-AA-301,[17] which showed a 4-month improvement in OS, whereas enzalutamide's approval was based on the AFFIRM trial,[18] which found a 4.8-month improvement in median OS. Following these initial registration studies, COU-AA-302[19] and MDV3100-03[20] demonstrated efficacy of abiraterone and enzalutamide in the prechemotherapy setting. Both studies improved radiographic progression-free survival (rPFS) and OS in asymptomatic and minimally symptomatic chemotherapy-naïve patients with mCRPC.[19,20] Specifically, the COU-AA-302 trial randomized 1088 asymptomatic to mildly symptomatic, chemotherapy-naïve patients without visceral disease to either abiraterone plus prednisone or placebo plus prednisone. Compared with the placebo group, abiraterone showed significant improvement in median OS (34.7 vs 30.3 months; HR, 0.81; $P = .0033$).[19]

Similarly, in the MDV3100-03 trial, 1717 asymptomatic-to-mildly symptomatic, chemo-naïve patients with mCRPC were randomized to either enzalutamide or placebo daily. Enzalutamide demonstrated improvement in both OS (HR, 0.71; 32.4 vs 30.2 months; $P < .0001$) and median rPFS (HR, 0.17; not reached vs 3.7 months; $P < .0001$) relative to placebo.[20] These results led to the approval of both abiraterone and enzalutamide in the prechemotherapy space in 2012 and 2014, respectively.[20,21] Given their more favorable adverse

event (AE) profile and relative ease of administration, AR-directed agents have replaced taxane chemotherapy as first- and/or second-line treatments for mCRPC.

Cross-resistance is commonly observed between abiraterone and enzalutamide when used sequentially for the treatment of mCRPC (ie, the use of one AR-directed therapy typically results in a decreased duration of response and blunted response to the next AR-targeted therapy). Thus, several studies have explored the optimal sequencing of abiraterone and enzalutamide in an attempt to maximize clinical efficacy.

A recent report presented at the 2017 American Society of Clinical Oncology Annual Meeting by the Kyoto-Baltimore Collaboration suggested that abiraterone as first-line treatment before enzalutamide prolonged combined prostate-specific antigen (PSA) PFS (HR, 0.56; *P* <.001), but not OS, relative to enzalutamide as first-line treatment before abiraterone.[22] However, the opposite trend was observed in another study, where enzalutamide as first-line treatment resulted in more patients experiencing >50% PSA reduction than with abiraterone (73% vs 53%; *P* = .004), but with no difference in time to PSA progression (TTPP).[23] In this study, baseline pathogenic circulating tumor DNA (ctDNA) alterations in *AR*, *TP53*, *RB1*, and DNA repair (*BRCA2*, *ATM*) genes were associated with a shorter TTPP.

In addition, a retrospective analysis of a real-world mCRPC database showed that treatment effect persistence was significantly longer in chemotherapy-naïve patients treated with enzalutamide relative to abiraterone (HR, 0.86; *P* = .02).[24] Despite the data presented here, there have been insufficient definitive evidence on the optimal sequencing of the 2 AR-directed agents, and a prospective, randomized clinical trial is needed in order to draw a definitive conclusion. Currently, the pattern for sequencing AR-targeted therapies is individualized, and it is dependent on clinical context, with considerations that include AE profile and baseline medical comorbidities. In the context of predictive biomarkers for AR-directed therapies, recent studies have shown that the detection of AR splice variant 7 on circulating tumor cells predicts for resistance to both AR-directed agents.[25]

Several recent trials have suggested improved survival with up-front utilization of docetaxel or abiraterone in metastatic castration-sensitive prostate cancer (mCSPC), when combined with ADT. The CHAARTED trial[5] of docetaxel enrolled 790 patients with mCSPC to ADT plus docetaxel or ADT alone. It found that ADT plus docetaxel prolonged OS by 13.6 months compared with ADT alone (57.6 vs 44.0 months; HR, 0.61; *P* <.001). The median time to biochemical, symptomatic, or rPFS was 20.2 months in the combination group compared with 11.7 months in the ADT-alone group (HR, 0.61; 95% CI, 0.51 to 0.72; *P* <.001).

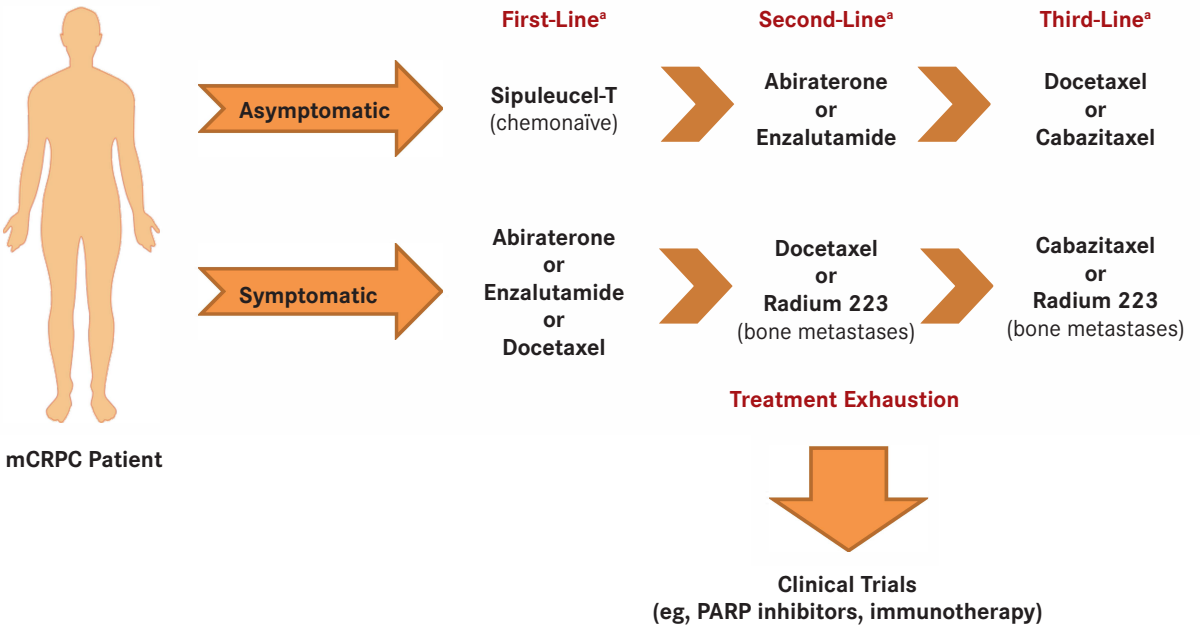
Recent studies have also established abiraterone plus ADT as a new standard of care for mCSPC.[4,26] The STAMPEDE trial[4] in CSPC demonstrated a 3-year OS of 83% versus 76% (HR, 0.63; *P* <.001) and failure-free survival of 75% versus 45% (HR, 0.29; *P* <.001) for ADT plus abiraterone versus ADT alone. In addition, the double-blind, randomized, phase III LATITUDE trial[27] reported results similar to those of the STAMPEDE trial. The LATITUDE trial studied 1199 men with mCSPC receiving either ADT plus abiraterone plus prednisone or ADT with dual placebos. It found that the treatment group had significantly longer median OS (not reached vs 34.7 months; HR, 0.62; *P* <.001) as well as rPFS (33 months vs 14.8 months; HR, 0.47; *P* <.001).[27]

In addition, an open-label, single-arm, phase II study evaluated the efficacy of enzalutamide in hormone-sensitive prostate cancer as a single agent without ADT.[28] At week 97 post treatment, 45 of a total 67 patients (67%) were still on enzalutamide, and all 45 had a PSA response (100%; 95% CI, 92%-100%). Of 26 patients who originally presented with metastases, 13 achieved a complete response (50%) and 4 (15.4%) demonstrated a partial response.[28] Taken together, these results highlight the positive clinical impact of using chemotherapy and AR-directed agent therapy for the upfront treatment of mCSPC, which will likely alter disease biology, clinical course, and sequencing of these agents in the mCRPC setting.

Prostate cancer most commonly metastasizes to the bone, resulting in significant morbidity due to pain and decreased quality of life.[29] For patients with symptomatic bone metastases but no visceral disease, the radionuclide radium-223 was FDA approved, based on data from the ALSYMPCA trial,[30] which showed a median OS benefit (HR, 0.7; 14.9 vs 11.3 months; *P* <.001) in 921 men with symptomatic bone metastasis, regardless of previous chemotherapy status. Due to its chemical structure and calcium-mimetic properties, radium is preferentially taken up in areas of increased bone turnover, such as bone metastases.[31] Following bone uptake, radium-223 emits cytotoxic alpha radiation, which has a shorter range of action than that of beta and gamma particles.[31] Therefore, the effect is more localized and targeted, leading to decreased bone marrow toxicity. While there are preliminary data showing clinical benefits of radium-233 as a first-line agent,[32] it is typically used as second- or third-line therapy to palliate symptomatic bone metastases on an as-needed basis.

Concomitant external-beam radiation therapy had a hematologic safety profile similar to that of radium-233 alone in a post hoc analysis evaluating safety, and this

FIGURE 2. Treatment Sequencing Strategy for Metastatic Castration-Resistant Prostate Cancer



[a]All treatment options should include androgen deprivation therapy (surgical/medical orchiectomy)

combination could be used for treatment of symptomatic bone metastases.[33] Radium-223 can be safely combined with abiraterone or enzalutamide, with these findings extending to patients who were asymptomatic at baseline.[34,35] Median OS was longer in patients who received radium-223 plus abiraterone, enzalutamide, or both relative to radium-223 without concomitant use of these agents (median NA [not available]; 95% CI, 16 months-NA vs median 13 months, 12-16 in radium-223 alone) and in patients who received radium-223 plus the RANK ligand inhibitor, denosumab (median NA, 15 months–NA), relative to patients who received radium-223 without denosumab (median, 13 months, 12 months-NA).[34,35] The findings of improved survival with concomitant treatment require confirmation in randomized trials.

In 2010, the FDA approved sipuleucel-T,[36] the first and only immunotherapy to receive FDA approval in mCRPC. Sipuleucel-T is a customized vaccine composed of a patient's own antigen-presenting cells (APCs), which are cultured ex vivo with a fusion protein of prostatic acid phosphatase (PAP) and granulocyte-macrophage colony-stimulating factor. The APCs are then re-infused into the patient to initiate PAP-directed T-cell antitumor response.[37] In the phase III IMPACT trial,[37] sipuleucel-T showed a median survival of 25.8 months versus 21.7 months in the placebo arm (n = 512; *P* = .03) in men with asymptomatic mCRPC. However, the feasibility of using sipuleucel-T in routine clinical practice has been controversial, given the inability to use PSA as a biomarker for treatment response, and given the vaccine's high cost and cumbersome preparation process. Clinical trial data exploring combinations of sipuleucel-T with other immunomodulatory agents in mCRPC are awaited.[38]

Neuroendocrine prostate cancer (NEPC) is a rare but lethal subtype of advanced prostate cancer.[39] It develops in a subset of patients with mCRPC after ADT, and has increased in emergence with the advent of AR-targeted therapies.[39] About 10% to 15% of patients with NEPC present de novo with the typical phenotype of small-cell lung carcinoma (SCLC)[39] This small-cell "AR-indifferent" subtype is treated with platinum- and etoposide-based chemotherapy, similar to treatment of SCLC,[40] and it does not fit the standard treatment sequence paradigm for mCRPC.

Sequencing of mCRPC Treatment

Based on limited data, we propose the following algorithm for sequencing therapies in mCRPC (**Figure 2**). For asymptomatic-to-mildly symptomatic patients with mCRPC, sipuleucel-T may be used as first-line therapy for asymptomatic, chemotherapy-naïve patients without any visceral disease, followed by AR-directed agents for the second line, and chemo agents as third line. For symptomatic patients, AR-directed agents are used in the

first line, followed by docetaxel for the second line and cabazitaxel in the third line once the patient has become resistant to docetaxel. There are no known differences in clinical outcomes regarding the use of taxanes or androgen-directed therapies as first-line treatments, but the latter are generally used in the first line due to their favorable AE profile and more convenient oral dosing schemes. In clinical practice, taxanes are commonly used in the first-line setting for symptomatic patients with rapidly progressive visceral/bone metastases, but evidence to support this strategy is lacking.

Alternatively, radium-223 can be used as a palliative therapy in patients who are presenting with symptomatic bone metastases, regardless of previous chemotherapy status. It is safe in combination with androgen-directed therapies, but the finding of improved OS needs confirmation in randomized trials. There are limited data on mCRPC treatment beyond the third line, leaving it to the discretion and experience of the treating physician to decide upon the optimal treatment plan. Notably, emerging data from tumor genomics suggest that tumor and germline sequencing may be invaluable in guiding future treatment choices, particularly as sequencing relates to defects in the DNA repair pathways that can be targeted with DNA-damaging agents, such as PARP inhibitors and platinum-based chemotherapy.

In a multicenter analysis of 692 patients with metastatic prostate cancer, 11.8% of patients were found to carry germline mutations in DNA-repair pathways.[41] In the phase II TOPARP trial of olaparib, a PARP inhibitor, 16 of 50 patients with mCRPC responded, and the majority of responders (88%) carried somatic alterations in homologous recombination-associated DNA-repair genes, such as *BRAC2* and *ATM*.[42,43]

Finally, immunotherapy clinical trials with immune checkpoint blockade therapies are revolutionizing cancer treatment, and they are beginning to show signs of clinical benefit in a subset of patients with mCRPC.[43] The future looks promising for the treatment of mCRPC.

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