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The Potential for Chemotherapy-Free Strategies in Advanced Prostate Cancer

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Key Words

Chemotherapy-free strategies • Advanced prostate cancer • Chemotherapy • Secondary hormonal treatment

Abstract

The treatment landscape for advanced prostate cancer is evolving rapidly, with new agents and strategies, and more optimal use of existing therapies under constant development. Efforts were focused on better understanding of the biology of the disease.This effort has paved the way for a more contemporary and effective therapies to be developed. There are now 6 FDA-approved therapies that increase overall survival. These include the immunotherapy sipuleucel-T; the 2 androgen pathway inhibitors: abiraterone acetate and enzalutamide; 2 chemotherapy drugs: docetaxel and cabazitaxel; and the radionuclide: radium-223. Advanced prostate cancer may be one of the few cancers for which multiple chemotherapy and nonchemotherapy regimens are considered as standard. Several recently published clinical trials have demonstrated the suprising activity of chemotherapy-free strategies, and we should not be too eager to discount these "old-fashioned" treatments. Optimal sequencing is still unclear because new therapies have proliferated so quickly that comparative data are limited. In this short communication, we identify current challenges and unmet needs in advanced prostate cancer and provide an overview of their respective clinical activity, while highlighting distinctions between therapies.

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Introduction

Prostate cancer is the most commonly diagnosed cancer in men in the worldwide and the second leading cause of cancer-related deaths. In 2017, almost 161,360 men in the United States received a diagnosis of prostate cancer, and approximately 26,730 men died of metastatic prostate cancer [1]. The leading cause of these deaths was metastatic spread. The risk of prostate cancer increases strikingly with age. The lifetime risk of a prostate cancer diagnosis is 1 in 6, and the risk of dying from prostate cancer 1 in 35 [2]. Prostate cancer is most often diagnosed in men age 55 to 74 years, and the median age at diagnosis is 66 years [3]. Metastases most commonly occur in bone, viscera, and lymph nodes and cause significant symptoms, including pain and fatigue [4, 5]. This situation negatively affect patient functioning, quality of life (QoL).

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Table 1. Phase III trials of chemotherapy-free strategies in mCRPC

Agent	Patient population	Study design	Administration	n	Primary end point	Secondary end point
Abiraterone	previously untreated	phase III	abiraterone 1,000 mg daily plus prednisone 10 mg daily or placebo plus prednisone	1,088	OS: 34.7 vs. 30.3 months (HR 0.81, 95%CI 0.70–0.93)	radiographic PFS: 16.5 vs. 8.2 months (HR 0.52, 95%CI 0.45–0.61)
Enzalutamide	previously untreated	phase III	enzalutamide or placebo	1,717	OS: 32.4 vs. 30.2 months (HR 0.71, 95%Cl 0.60–0.84)	radiographic PFS: 20 vs. 5.4 months (HR 0.32, 95%CI 0.28–0.36)
Abiraterone	prior docetaxel chemotherapy	phase III	abiraterone (1,000 mg/d) plus prednisone (5 mg twice a day) or placebo plus prednisone	1,195	OS: 15.8 vs. 11.2 months (HR 0.74, 95%CI 0.64–0.86)	radiographic PFS: (5.6 vs. 3.6 months, $p < 0.0001$), improved time to PSA progression (10.2 vs. 6.6 months, $p < 0.0001$), and produced more PSA responses (38 vs. 10%, $p < 0.0001$)
Enzalutamide	prior docetaxel chemotherapy	phase III	enzalutamide (160 mg as a single dose, once daily) or placebo	1,199	OS: 18.4 vs. 13.6 months (HR 0.63, 95%CI 0.53–0.75)	enzalutamide was significantly better than placebo including PSA response (> 50% decrease, 54 vs. 2% of patients) radiographic PFS (8.3 vs. 2.9 months, HR 0.25, $p < 0.0001$)
Sipuleucel-T	chemotherapy naïve (85% of patients)	phase III	sipuleucel-T or to placebo	512	OS: 25.8 vs. 21.7 months (HR 0.78, 95%CI 0.61–0.98)	PFS was not significantly prolonged (14.6 vs. 14.4 weeks)
Radium-223	patients who have previously received docetaxel and who did not	phase III	radium-223 vs. placebo	921	OS: 14.9 vs. 11.3 months (HR 0.70, 95%CI 0.58–0.83)	the time to first symptomatic skeletal event was significantly increased (15.6 vs. 9.8 months, HR 0.66, 95%CI 0.52–0.83)

The emergence of new agents for advanced prostate cancer has resulted in multiple treatment options, requiring careful decision making for individual patients. Prostate cancer may be one of the few cancers for which multiple chemotherapy and nonchemotherapy regimens are considered as standard. Clinicians face the increasingly difficult task of choosing from multiple potentially effective treatments that are also costly and potentially toxic. The "right treatment" though, wasn't going to be easy. What works for one person might not work for another. Over the past decade, 4 nonchemotherapy options have been approved by the US Food and Drug Administration (FDA) and/or the European Medicines Agency for treatment of metastatic prostate cancer (table 1). These have included enzalutamide and abiraterone, the 2 agents designed specifically to affect the androgen axis [6, 7]; sipuleucel-T, which stimulates the immune system [8]; and radium-223, a radionuclide therapy [9].

One of the goals of therapy is for patients to receive as many lines of therapy as possible, without compromising QoL. In reporting differences in nonchemotherapy options, we have attempted to be objective but have included our perspective.

Why is There a Need for Nonchemotherapy Options? Patient and Physician Perceptions

Treatment decision making for prostate cancer is complex for both patients and physicians. The goal of the therapy in metastatic prostate cancer is to extend

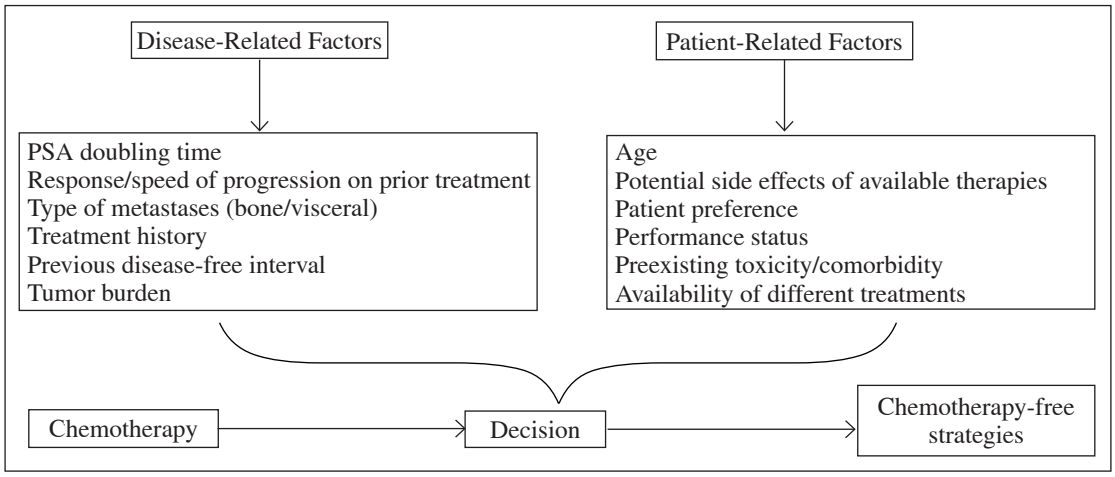


Fig. 1. Decision factors for the treatment of metastatic prostate cancer.

overall survival (OS) with as few prostate-related symptoms and treatment-related side effects. Much is made of the need to individualize cancer therapy, particularly for a disease like metastatic prostate cancer, where an array of treatments are available when choosing an ideal therapeutic strategy. Without questions, chemotherapy is active in metastatic prostate cancer. Docetaxel is the standard first-line chemotherapy for metastatic castration-resistant prostate cancer (mCRPC). It prolongs progression-free survival (PFS) and OS, ameliorates pain, and improves QoL [10]. Cabazitaxel has emerged as a second-line chemotherapy option for patients with mCRPC who have had progressive disease during or after docetaxel treatment [11]. Cytotoxic chemotherapy is associated with well-documented toxicities. Toxicity of docetaxel includes myelosuppression, fatigue, peripheral edema, neurotoxicity, hyperlacrimation, and nail dystrophy. Toxicity of cabazitaxel includes neutropenia (including febrile neutropenia) and diarrhea. Elderly men with a limited life expectancy and/or associated comorbidities could be considered ideal candidates for nonchemotherapy options.

Where is There a Role for Nonchemotherapy Treatment of Metastatic Prostate Cancer?

We will have to weigh the pros and cons of each approach in terms of the duration of therapy, side effects, and cost when deciding which course is best suited for CRPC patients.

New studies provide a useful information on how to personalize management and how to select and sequence existing therapies. Use of newly approved therapies must be balanced against many other factors (fig.1). We tailor the regimen to give them the most effective therapy that also works with their lifestyle. Using these precepts, it is possible to divide treatments into those that control pain or symptoms, those that delay the development of skeletal-related events, and those that delay death rather than those that achieve reductions in prostate specific antigen (PSA) levels, tumor shrinkage, favorable bone scans, or reductions in circulating tumor cells (fig .2).

The novel agent abiraterone acetate is an orally administered small molecule that irreversibly inhibits the products of the CYP17 gene (including both 17,20-lyase and 17-alpha-hydroxylase). It stops production of testosterone throughout the body, reducing hormone levels still further. Enzalutamide is a potent oral nonsteroidal AR signaling inhibitor [12]. Both abiraterone and enzalutamide have demonstrated improved survival in chemotherapy-naive men with asymptomatic or minimally symptomatic disease [13, 14], as well as in those who had previously received docetaxel [6, 7]. While generally well tolerated, abiraterone can result in mineralocorticoid excess due to its inhibitory effect on steroid metabolism, leading to fluid retention, hypokalemia and hypertension but it respond to low dose glucocorticoids. Abiraterone cannot be used in patients with severe liver dysfunction. The most common side effects of enzalutamide are fatigue, hypertension, cognitive and mood impairment and hot falls. Seizures occurred in clinical trials of this

agent, but in less than 1% of patients. Enzalutamide has an interaction with warfarin by decreasing exposure to warfarin. Consider new hormonal manipulations before initiation of cytotoxic chemotherapy, especially in men with mCRPC or in those who are asymptomatic. Unlike abiraterone, enzalutamide does not require concurrent corticosteroid administration.Corticosteroids may be relatively contraindicated in some men owing to its effect on muscle strength, glycemic control, weight control, skin integrity and bone density. If you have to choose between abiraterone and enzalutamide, what is your preferred first-line choice for men with mCRPC with no contraindication to either drug? Abiraterone plus prednisone, and enzalutamide have not been directly compared with each other. There is no clear distinction as to which agent should be used first with regard to the hormonal agents. The choices can be narrowed down further based on toxicity profiles considerations. For example; abiraterone should not be used in patients with cardiovascular disease, such as heart failure, recent myocardial infarction, or ventricular arrhythmia. Enzalutamide should not be recommended in patients with history of falls, baseline significant fatigue and baseline significant neurocognitive impairment.

No comparative studies have been conducted with docetaxel against new hormonal treatments in the CRPC. Because the populations of patients are usually heterogeneous it is difficult to compare the results of different treatments. It is no surprise that incorporation of nonchemotherapy drugs into standard docetaxel regimen might be the most natural first step after this. This approach may have a synergistic effect. It is likely that some patients with CRPC might do well regardless of the choice of chemotherapy or nonchemotherapy. Initial androgen deprivation therapy (ADT) failure < 16 months' response, PSA doubling time < 6 months, pain requiring opiates, increase in number and pattern of metastases, the Eastern Cooperative Oncology Group performance status ≤ 1 have been associated with poor outcomes [15–17]. At this stage, whether nonchemotherapy agents can overcome some, all, or any of these adverse factor are unclear. Ongoing prospective studies integrating novel imaging and molecular analyses will allow for more personalized risk assessment and recommendations for chemotherapy-free strategies.

Sipuleucel-T, an autologous cellular immunotherapy, is the first therapeutic anti-cancer vaccine to receive FDA approval. It prolonged OS compared with placebo in randomized trials in men with minimally symptomatic mCRPC [8]. Patients with visceral metastases or requiring opioid analgesics were excluded from this study. The optimal scenario in which to administer this agent is when disease burden and PSA are low [18–20]. The treatment was well tolerated, with adverse events largely related to infusion of the vaccine and consisting of fevers, chills, fatigue, nausea, and headache. Earlier use of sipuleucel-T prior to abiraterone/enzalutamide is preferred, given lack of short-term benefits on PSA, disease control, and possible improved survival impact earlier in the disease course [20].

The radiopharmaceutical agent radium-223 emits alpha-radiation and selectively targets bone. In a phase III trial, treatment with radium-223 was well tolerated and increased both OS and time to first symptomatic skeletal-related event in patients with symptomatic bone metastases and no known visceral metastases [9]. There are no randomized trials that compare radium-223 with other agents known to prolong OS in patients with mCRPC. Patients should be followed carefully for bone marrow toxicity prior to dosing and over time.

What is the Optimal Systemic Treatments for Men with Metastatic Hormone-Sensitive Prostate Cancer? Is Docetaxel or Chemotherapy-Free Strategies the Right Question?

Prostate cancer heterogeneity may be better addressed by a combination strategy upfront docetaxel in M1 systematic review and meta-analysis (CHAARTED, STAMPEDE, and GETUG-AFU15 trials) showed an absolute improvement in 4-year survival of 10% from the combination of docetaxel and ADT in metastatic hormone-sensitive prostate cancer [21–23]. Two recently published phase III randomised controlled trials – LATITUDE [24] and STAMPEDE [25] trials – have assessed the efficacy of abiraterone and prednisone plus ADT versus ADT alone in castration-sensitive metastatic prostate cancer and in newly diagnosed metastatic prostate cancer, and node-positive and high-risk locally advanced non-metastatic prostate cancer, respectively. STAMPEDE trial represents a 37% improvement in survival (HR 0.63, 95%Cl 0.52–0.76).

In hormone naïve prostate cancer abiraterone acetate + prednisone improves OS by 37%, failure free survival by 71%, symptomatic skeletal events by 55%. LATITUDE trial represents a statistically significant 38% risk reduction of death (HR 0.62, 95%Cl 0.51–0.76). Radiographic PFS was significantly improved with the addition of abiraterone (median 33.0 vs. 14.8 months, HR 0.47, 95%CI

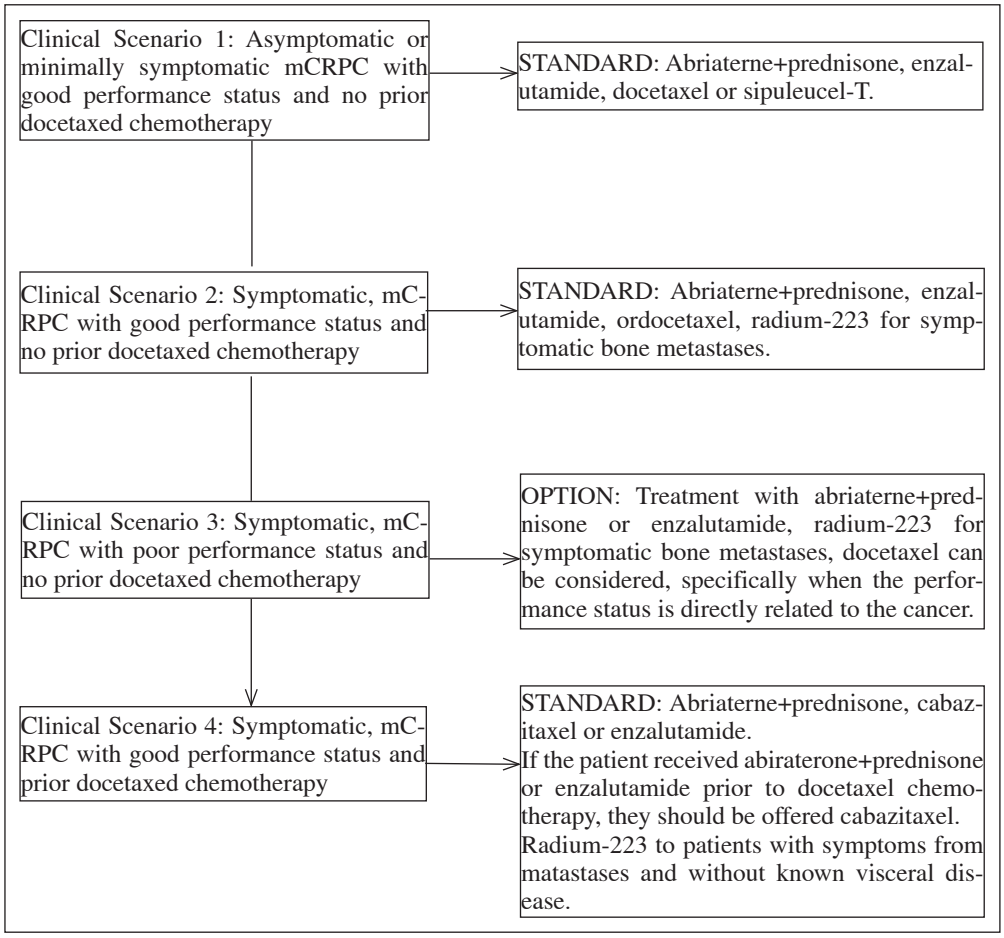


Fig. 2. Personalized therapy in advanced-stage prostate cancer: current therapeutic landscape.

0.39–0.55). A systematic review and meta-analysis have shown that adding abiraterone acetate to ADT provides highly significant and substantial reductions in the risk of both death (38%) and clinical/radiological PFS (55%) for men with metastatic hormone-sensitive prostate cancer. These translate into 14% absolute improvements in OS at 3 years after randomization. Will it be maintained at 4 years? The addition of androgen pathway inhibitors to standard ADT has already demonstrated an ability to improve outcomes, and more studies are ongoing.

ADT + abiraterone or ADT + docetaxel are both standard of care in metastatic hormone-sensitive prostate cancer. These findings raise the new question as to which patients are most likely to benefit from either treatment approach, and under what circumstances should the combination approach be considered standard.

Which combination regimen for newly diagnosed metastatic prostate cancer? Recruitment to docetaxel + prednisone and abiraterone + prednisone overlapped in STAMPEDE giving the only head-to-head evidence comparing these 2 new standard treatment approaches. The evidence from directly randomized data comparing these 2 therapies showed no evidence of a difference in overall or prostate cancer-specific survival, nor in other important outcomes such as symptomatic skeletal events [26]. Patients likely to gain access to other treatment if first stops working. Abiraterone may have fewer toxicities and may be more convenient to administer. Docetaxel may be less expensive and has a shorter time of treatment, but it is clearly more toxic. Abiraterone may have the benefit of improved tolerability over a short course versus chemotherapy but does require a much more ex-

tensive duration of use and further mandates concomitant intake of prednisone. It does require that clinicians be able to discuss both of the options with their patients carefully. The current challenge is to identify the best combination of treatments to achieve long-term control.

Conclusions

We have known that prostate cancer biology is heterogeneous. This heterogeneity has paved the way for multiple novel therapies to be developed. However, there is a need for a range biomarkers that determine who needs treatment, the effectiveness and clinical benefit of treatment. New agents have distinctive toxicities. Importantly, chemotherapy-free strategies have improved outcomes but access to medications is an issue around the world and especially so in low- and middle-income countries. Emerging trials and biomarkers may help decision making about switching to another androgen-based therapy or toward chemotherapy. We had nothing happening for 10 years, at least clinically, from the time that docetaxel was approved until 2010 with cabazitaxel, sipuleucel-T, radium-223, abiraterone, and enzalutamide all approved in succession. Outcomes are encouraging. The problem now is, what is the rational sequence? Should you be using 2 androgen receptor pathway inhibitors at the same time? Is that better than just simply using one or doing them sequentially? As drug development continues to accelerate and we acquire a wider breadth of therapy options, design trials will be needed to answer questions regarding that show how to maximize patient benefit with these new nonchemotherapy treatment in clinical practice. To achieve that aim, we will need rational combinations of new drugs, regardless of how we call them.

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