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Sequencing Treatment for Castration-Resistant Prostate Cancer

Catherine E. Handy, M.D., M.P.H.[1]
Emmanuel S. Antonarakis, M.D.[2,*]

Address
[1]Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, 600 N. Wolfe Street, Harvey 306, Baltimore, MD, 21287, USA
[*,2]Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, 1650 Orleans Street, CRB1 - Room 1M45, Baltimore, MD, 21287, USA
Email: eantona1@jhmi.edu

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Opinion statement

Prostate cancer is the most common non-cutaneous cancer diagnosed in men and the second leading cause of male cancer deaths in the USA. While most cases are diagnosed in early stages, some will present as or progress to metastatic disease and eventually castration-resistant prostate cancer (mCRPC) which has a mortality rate exceeding 50 %. There are currently six approved systemic life-prolonging therapies for use in mCRPC, yet little data to guide sequencing. Clinical factors, including the presence or absence of symptoms and the presence or absence of visceral metastases, should help determine the best therapeutic choice at each treatment node. Those with asymptomatic bone-only disease could be considered for sipuleucel-T, abiraterone, enzalutamide, or docetaxel in the first-line setting. For symptomatic disease, docetaxel could be used or radium-223 if disease is only present in the bone. In the second-line setting, sipuleucel-T or radium-223 can be used in the appropriate clinical setting. Taxane chemotherapy could be used if a novel androgen-directed therapy was used in the first-line setting. Cabazitaxel, if docetaxel was previously used, should be considered. There is scarce data on best treatment options in the third-line setting. In general, we recommend alternating between androgen-targeting agents and taxane chemotherapy. Finally, consideration should be given to testing for the androgen receptor splice variant AR-V7, which may be a relevant treatment-specific biomarker to aid in the selection of androgen-targeting therapy versus chemotherapy at each treatment juncture. Mutation testing for DNA damage repair defects can also be considered, as such patients may benefit from investigational poly ADP ribose polymerase (PARP) inhibitors or platinum-based chemotherapies. Several ongoing studies have been designed to answer some of these sequencing questions, including the biomarker questions, and will hopefully continue to inform us about rational therapy selection in mCRPC.

Introduction

Prostate cancer is the most common non-cutaneous cancer diagnosed in men and the second most common cause of male cancer deaths in the USA [1]. Worldwide, it is the second most common cancer diagnosed and is the fifth leading cause of cancer death in men [2]. Most men who are diagnosed with prostate cancer present with apparent localized disease [3]. Despite initial treatment, some of these men will go on to have progressive disease; first with biochemical recurrence, where prostate specific antigen (PSA) is detected but there is no clinical or radiographic evidence of disease, and then many continue to progress and develop distant metastatic disease [4]. Other patients present with de novo metastatic disease at the time of the first diagnosis. Treatment for advanced disease usually begins with androgen deprivation therapy to achieve castrate levels of testosterone because growth of prostate cancer cells relies, initially, on androgen receptor (AR)-driven mechanisms [5]. Virtually, all men with metastatic prostate cancer will then also progress to castration-resistant disease with a mortality rate of over 50 % [4].

There are currently six systemic therapies approved by the Food and Drug Administration (FDA) that offer a survival benefit for the treatment of metastatic castration-resistant prostate cancer (mCRPC) [6]. These include docetaxel, cabazitaxel, enzalutamide, abiraterone acetate, sipuleucel-T, and radium-223. There is little data to guide the rational sequencing of these drugs, however. Clinical trials to help answer this question are ongoing, and some examples are listed in Table 1. Here, we will review the current evidence and offer suggestions for sequencing of systemic therapy in mCRPC. This review is organized by line of therapy (i.e., first line, second line, third line, and beyond), consistent with recent recommendations from the Prostate Cancer Working Group 3 (PCWG3) guidelines [7]. We also offer our personal preferences for treatment selection where evidence is lacking.

First-line therapy

Chemotherapy

The TAX-327 trial was a pivotal study investigating the use of chemotherapy for the treatment of mCRPC. This trial compared mitoxantrone, one of the earliest approved therapies for advanced prostate cancer (but offering no survival benefit) against two docetaxel regimens. In this study of 1006 men, it was shown that docetaxel, given every 3 weeks, prolonged survival by 2.9 months with the trend persisting across older and younger patients, those with pain and those with higher PSA values [8, 9]. In addition to the survival benefit in the docetaxel group, there was also more pain reduction and an improved quality of life. An important note when considering treatment with docetaxel is that most men included in the trial had a very good performance status with 90 % of men having a Karnofsky score >70, and this study included men with bone metastases (90 % of men) as well as men with visceral metastases (20–25 %) [8, 9].

The second pivotal trial showing the benefit of docetaxel in the first-line mCRPC setting was the SWOG-9916 trial, a study of 674 men treated with docetaxel (and estramustine) versus mitoxantrone, and demonstrated a 1.9-month improvement in survival in the docetaxel arm [10]. Ninety percent of patients in this study had a good performance status (Eastern Cooperative Group (ECOG) performance status of 0 or 1), and while 85–90 % had bone disease, 40 % had lymph node or visceral metastases [10]. Based on these two studies, docetaxel is a very reasonable first-line therapy in chemofit mCRPC patients, especially in men with symptomatic disease (e.g., bone pain) and/or those with bulky visceral metastases.

Cabazitaxel, a novel taxane chemotherapy that was approved in the post-docetaxel setting, has also been studied in chemotherapy-naïve patients, with a

Table 1. Selected clinical trials examining optimal sequencing of therapy in metastatic castration-resistant prostate cancer

Trial identifier	Phase	Title (and sample size)	Description of study
NCT02125357	2	Sequencing abiraterone and enzalutamide in mCRPC (*N* = 118)	Randomized controlled trial to evaluate the effects of sequencing novel hormonal therapies: abiraterone versus enzalutamide followed by crossover to the alternative agent after progression
NCT02254785	2	Cabazitaxel vs abiraterone or enzalutamide in patients with poor-prognosis mCRPC (*N* = 120)	Randomized controlled trial to compare the response to cabazitaxel or novel hormonal agents (abiraterone or enzalutamide) as initial therapy in patients with mCRPC and poor prognostic features
NCT02485691	3	CARD: cabazitaxel vs switch to alternative AR-targeted agent (abiraterone or enzalutamide) in mCRPC patients previously treated with docetaxel and who rapidly failed a prior AR-targeted agent (*N* = 324)	Randomized controlled trial to compare the response to cabazitaxel versus AR-targeted therapy (abiraterone or enzalutamide) in mCRPC patients who have been previously treated with docetaxel and who had disease progression within 12 months of starting novel AR-targeted therapy
NCT02793765 and NCT02793219	2	Docetaxel followed by sipuleucel-T in mCRPC (*N* = 32) and sipuleucel-T followed by docetaxel in mCRPC (*N* = 32)	Two parallel single-arm trials by the same investigators: one to evaluate the role of sequential docetaxel followed by sipuleucel-T for patients with mCRPC and the other to evaluate the role of sequential sipuleucel-T followed by docetaxel

direct comparison to docetaxel. In the FIRSTANA trial, designed as a superiority trial comparing docetaxel versus cabazitaxel, 1168 men with mCRPC and ECOG performance status of 0–2 were randomized to docetaxel or one of the two different doses of cabazitaxel [11••]. The primary end point of overall survival was not significantly different between the groups (HR 1.01, $p = 0.99$ comparing docetaxel to cabazitaxel 20 mg/m^2; HR 0.97, $p = 0.76$ comparing docetaxel with cabazitaxel 25 mg/m^2). There was also no significant difference in progression-free survival (4.4 months for cabazitaxel 20 mg/m^2, 5.1 months for cabazitaxel 25 mg/m^2, and 5.3 months for docetaxel), and frequency of adverse events were similar between the lower dose of cabazitaxel (41 %) and docetaxel (45 %) groups [11••]. Based on these results, there is insufficient data to currently support using cabazitaxel in the first-line mCRPC setting. One exception to this rule is in men who previously received docetaxel as part of a chemohormonal strategy for metastatic hormone-sensitive disease, in which case cabazitaxel could be justified after subsequent progression to mCRPC.

Novel androgen-directed agents

Abiraterone and enzalutamide were initially approved for use in the post-docetaxel treatment setting (COU-AA-301 and AFFIRM studies, respectively) [12, 13]. Abiraterone was first shown to prolong overall survival in the first-line

mCRPC setting in the COU-AA-302 trial [14]. This study included 1088 asymptomatic or mildly symptomatic men with ECOG scores of 0–1. They were treated with abiraterone or placebo (plus prednisone in both groups). Importantly, treatment was not compared to another standard therapy, and the study did not include men with visceral metastases. Abiraterone did demonstrate a 4.3-month overall survival improvement in this setting [14].

Enzalutamide was shown to be beneficial in the first-line setting in the PREVAIL study [15]. Participants included had a good performance status (ECOG 0–1) and not more than minimal symptoms from their disease. This study, which was a true placebo-controlled trial, showed a 2.2-month improvement in overall survival in the enzalutamide arm [15]. Both of these trials justify the use of the novel androgen-directed agents in the first-line mCRPC setting.

Enzalutamide has also been compared to bicalutamide in the first-line setting in two studies. In the STRIVE Trial, 257 men with CRPC were randomized to enzalutamide or bicalutamide. The primary end point was progression-free survival and included patients with non-metastatic disease. In the pre-specified subgroup with metastatic disease, the median progression-free survival was 16.5 months with enzalutamide versus 5.5 months with bicalutamide (HR 0.24, 95 % CI 0.17–0.34) [16], demonstrating that enzalutamide is superior to bicalutamide in this setting. The TERRAIN study included 375 men with mCRPC who had asymptomatic or minimally symptomatic disease. The primary end point was progression-free survival and it showed a 9.9-month improvement (15.7 months with enzalutamide versus 5.8 months with bicalutamide) [17]. Based on these two studies, it is reasonable to bypass bicalutamide and proceed directly with enzalutamide if this therapy is being considered for first-line treatment of mCRPC (of note, enzalutamide does not have an indication in non-metastatic CRPC).

Immunotherapy

Sipuleucel-T, an immunotherapy produced from autologous activated mononuclear cells, was one of the first cancer vaccines to be approved by the FDA [18]. Men with symptomatic disease (i.e., requiring narcotic pain medication) or visceral metastases were excluded from trials with sipuleucel-T. There were three trials done, all placebo-controlled, in the early treatment setting, where fewer than 15 % of the men had received prior chemotherapy. The first study included 127 men with asymptomatic mCRPC and showed no difference in progression-free survival ($p = 0.052$) but did suggest an overall survival benefit with median survival of 25.9 months in the treatment arm versus 21.4 months in the placebo arm ($p = 0.01$) [19]. A second trial included a total of 225 men, randomized in a 2:1 fashion to sipuleucel-T or placebo [20]. The integrated analysis of these two studies showed a survival benefit of 4.3 months (23.2 months in treatment versus 18.9 months in placebo arm, $p = 0.01$) despite no difference in median progression-free survival ($p = 0.11$) [20]. These findings were confirmed in the pivotal IMPACT study, which randomized 512 men with asymptomatic mCRPC to sipuleucel-T or placebo [21]. This study chose overall survival as its primary end point, and this end point was met with a 4.1-month improvement in median overall survival (HR 0.78, $p = 0.03$). Based on the current evidence, the authors recommend using sipuleucel-T before

docetaxel and before novel androgen-directed therapies in the first-line mCRPC setting, although its use in later lines of therapy is also reasonable.

Radiopharmaceuticals

Radium-223 is an alpha-emitting bone-seeking radionuclide, first considered to be used for the treatment of skeletal metastases [22]. The ALSYMPCA trial was a large phase 3 clinical trial examining the survival benefit of radium-223 in 921 men with mCRPC who had symptomatic bone metastases (requiring analgesics or radiation therapy for bone pain). Men who ever had visceral metastases or who had lymphadenopathy >3 cm were excluded. Additionally, men who needed blood transfusions or erythropoietin-stimulating agents were excluded due to the bone marrow-suppressing toxicities [23]. In this trial, about 40 % of men did not receive prior chemotherapy because either they were not chemofit or they declined chemotherapy. In the pre-specified subgroup analysis of those pre-chemotherapy patients, an overall survival benefit of 4.6 months was demonstrated [24]. Therefore, although radium-223 is most often used as a second- or third-line therapy for mCRPC, it is reasonable to use it in bone-predominant, symptomatic disease even in the pre-docetaxel setting.

Summary of the first-line therapy

There are a number of treatment options for the first-line therapy in men with mCRPC (Fig. 1). In those with a good performance status, patients with visceral

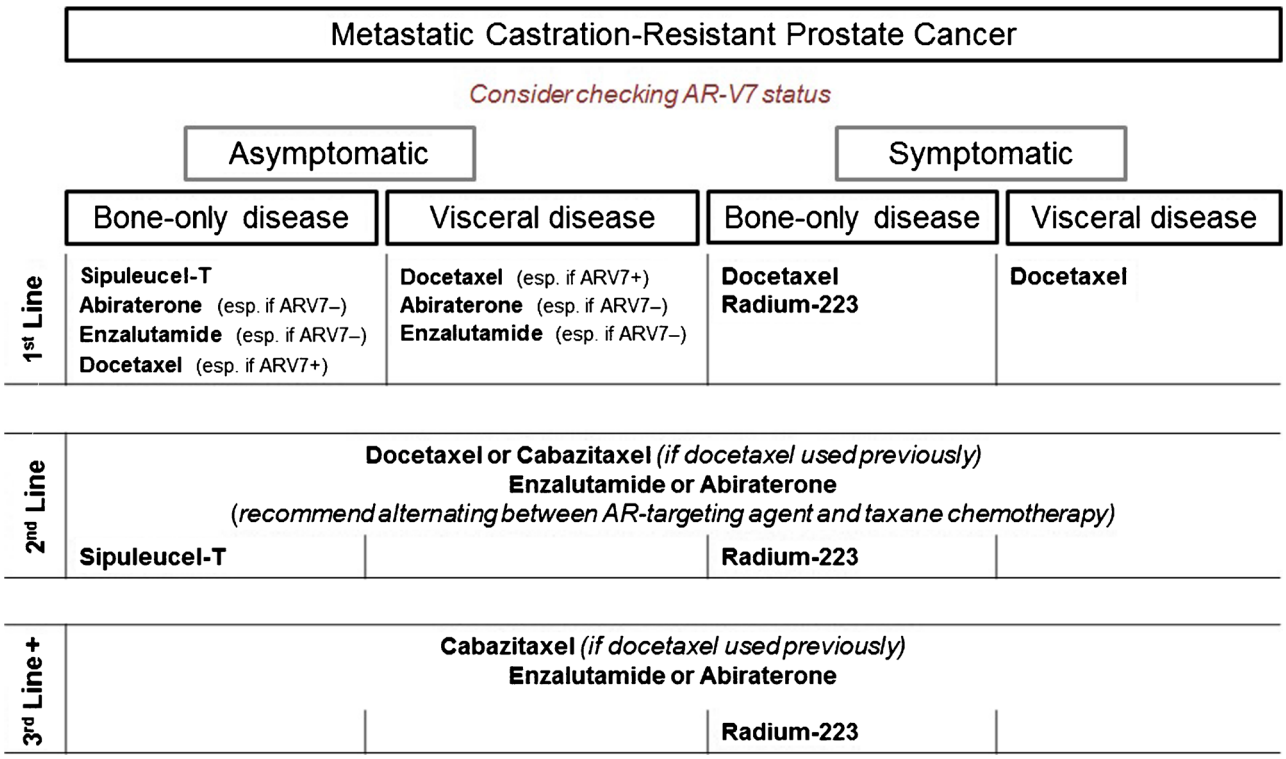

Fig. 1. Suggested treatment algorithm for sequential therapy in metastatic castration-resistant prostate cancer.

disease or with symptomatic disease, docetaxel chemotherapy may be a very reasonably initial option. Enzalutamide, abiraterone, and sipuleucel-T are also good options for treatment of patients with minimal to no symptoms. Those without symptoms and without visceral metastases should be considered for sipuleucel-T. However, those agents have only been compared to placebo in the first-line setting, so it is unknown which is superior to the other. Finally, for those with symptomatic bone disease and no visceral disease (or bulky lymphadenopathy), radium-223 could also be considered.

Additional considerations

Based on the results of the CHAARTED Trial [25], a study evaluating the benefit of docetaxel in hormone-sensitive metastatic prostate cancer patients, many men may be getting up-front docetaxel treatment prior to development of castration resistance. Retreatment with docetaxel at time of castration-resistant disease could be considered although this is not well studied. A small series of 98 patients with a previous response to docetaxel who were subsequently retreated showed that 57 % of patients were able to achieve disease control with retreatment [26]. Alternatively, cabazitaxel could be used in the post-chemohormonal therapy setting.

Another consideration is combination therapy with the above drugs. Radium-223 has been tested in combination with other first-line agents. For example, there are data from a small study of 53 patients with >2 bone metastases, combining docetaxel with radium-223. This trial suggested a longer PSA progression-free survival (24 versus 12 months) and a longer progression-free survival (18 versus 9 months) with the combined treatment compared to docetaxel alone [27]. Radium-223 is also being studied in combination with abiraterone [28], and the A031201 trial is exploring if abiraterone and enzalutamide given together in the first-line setting are superior to enzalutamide alone [29].

Second-line therapy

Chemotherapy

Docetaxel

Most of the data from docetaxel in the second-line setting comes from retrospective analyses. The largest retrospective study to look at docetaxel after abiraterone was a post hoc analysis of the COU-AA-302 trial since 47 % of the men who progressed after abiraterone treatment were then treated with chemotherapy (261 men received docetaxel and 4 received cabazitaxel) [30]. In that subgroup of patients, there was still reasonable activity of docetaxel with 7.6 months of progression-free survival and a PSA response rate of 50 % [30].

There have also been a number of smaller retrospective studies examining docetaxel after abiraterone. A retrospective review from Canada of 37 men who were treated with docetaxel after abiraterone showed a survival of 11.7 months and progression-free survival of 4 months, and this seemed to be independent of whether or not patients had a response to abiraterone in the first-line setting [31]. One small review with 23 patients treated with docetaxel after abiraterone showed that 65 % of patients had a PSA decline of at least 30 % and 48 % had a PSA decline of at least 50 % [32].

There have been some suggestions of cross-resistance between agents. In a study of 119 men who received abiraterone before docetaxel, PSA progression-free survival and progression-free survival were shorter (4.1 and 4.4 months) compared to the group that only received docetaxel (6.7 and 7.6 months, respectively) [33]. The authors also showed a PSA response to docetaxel in only 38 % of men, compared to a response of 63 % in men with no prior abiraterone treatment [33]. However, in another retrospective review of 198 patients who either received docetaxel followed by abiraterone ($n = 161$) or abiraterone followed by docetaxel ($n = 37$), there was no significant difference in median survival (31.4 versus 38.6 months) [34]. Another retrospective review compared 26 patients who received docetaxel followed by abiraterone to 32 patients who received abiraterone followed by docetaxel and also found no significant difference in combined progression-free survival (HR 0.82, $p = 0.41$) or overall survival (HR 0.79, $p = 0.31$) [35]. Therefore, while the efficacy of docetaxel may potentially be somewhat blunted when given after novel androgen-directed agents, it still retains sufficient clinical activity to justify its use as the second-line systemic therapy for mCRPC.

Cabazitaxel

The pivotal trial showing the benefit of cabazitaxel was done in the second-line treatment setting. The trial, called TROPIC, included 755 men previously treated with docetaxel and with good performance status (ECOG 0–2) [36]. Twenty-five percent of participants had visceral metastases and 45 % had symptomatic disease [36]. The study compared cabazitaxel to mitoxantrone and showed a significant improvement in survival by 2.4 months (15.1 versus 12.7 months) [36]. This study solidified the use of cabazitaxel in the post-docetaxel mCRPC setting, and this agent should currently not be used in men who have not previously received docetaxel.

There have been retrospective reviews exploring the timing of cabazitaxel compared to the novel anti-androgens in the second-line setting. The largest was a retrospective study of 350 men previously treated with docetaxel. Two hundred nineteen patients received abiraterone in the second-line setting and 131 received cabazitaxel. Overall survival was significantly greater when cabazitaxel was used instead of abiraterone in the second-line setting (HR 0.13, 95 % CI 0.02–0.73), and those who received cabazitaxel were able to receive more cabazitaxel when used in the second-line setting [37]. This finding may have been mediated by the observation that more drug was given in the second-line setting and that was possibly why there was improved overall survival with cabazitaxel [37].

A smaller retrospective study of 56 men showed no difference in progression-free survival in men treated with cabazitaxel compared to abiraterone in the second-line setting (5.9 months with cabazitaxel versus 6.7 months with abiraterone) [38]. Finally, a retrospective review from the Netherlands included 63 men who received docetaxel followed by cabazitaxel in the second-line setting followed by abiraterone as the third-line therapy and 69 men who received docetaxel followed by abiraterone and then cabazitaxel. There was no significant difference in median overall survival (19.1 months with cabazitaxel versus 17.0 months with abiraterone) but there was perhaps longer progression-free survival in patients treated with cabazitaxel in the second-line setting (9.5 versus 7.7 months, $p = 0.024$) [39].

Novel androgen-directed agents

Abiraterone was initially studied in the second-line setting, after docetaxel. The COU-AA-301 trial included 1195 men, ECOG score 0–2, who were randomized to abiraterone plus prednisone versus prednisone alone. Approximately 50 % of patients had nodal or visceral disease. Compared to placebo, abiraterone prolonged survival by 4.6 months (15.8 versus 11.2 months) and also prolonged PSA progression-free survival (8.5 versus 6.6 months) and radiologic progression-free survival (5.6 versus 3.6 months) [40].

Enzalutamide was also initially shown to be beneficial in the post-docetaxel setting. The AFFIRM trial included 1199 men, ECOG score 0–2, who were randomized to enzalutamide or placebo. Men with prior history of seizures or risk factors for the development of seizures were excluded. Enzalutamide was shown to provide a 4.8-month survival benefit compared to placebo, along with additional improvements in other pre-specified secondary end points including PSA response, progression-free survival, and quality-of-life metrics [13].

There have been a few retrospective studies looking at enzalutamide in the second-line setting after abiraterone. In one review of 150 patients, 40 % of patients treated with enzalutamide after abiraterone had a PSA response of at least 30 %. Thirty percent of patients who did not have an initial response to abiraterone did have a subsequent PSA response to enzalutamide [41].

Another review of 115 men who received enzalutamide after abiraterone in the second- or third-line setting showed that there was still some anti-tumor activity. The comparison between the 68 men who received enzalutamide in the second-line setting and the 47 men who received enzalutamide in the third-line setting showed no statistically significant differences in PSA response rates (22 versus 26 %), progression-free survival (4.6 versus 6.6 months), or overall survival (10.6 versus 8.6 months) [42].

Finally, a retrospective review of 61 men treated with enzalutamide compared to docetaxel in the second-line post-abiraterone setting showed no difference in outcomes with median progression-free survival of 4.7 months in the enzalutamide second-line treatment group versus 4.4 months in the docetaxel second-line treatment group [43].

Immunotherapy

In the IMPACT trial, approximately 15 % of patients who were randomized to sipuleucel-T or placebo had received previous chemotherapy. Five hundred and twelve men were randomized and all had a good performance status with ECOG 0–1, with asymptomatic disease and no visceral metastases. The results of this trial showed a 4.1-month improvement in overall survival when compared to placebo (25.8 versus 21.7 months) for the overall population [21]. Since a subset of patients on the IMPACT study had received prior docetaxel, sipuleucel-T might be a reasonable option in the post-docetaxel mCRPC setting as long as the patient remains asymptomatic or minimally symptomatic and without visceral or bulky lymph node metastases.

Radiopharmaceuticals

In the ALSYMPCA trial, 921 symptomatic men with bone-predominant disease were randomized to receive radium-223 or placebo and most were treated in the second-line post-docetaxel setting. The results of this trial showed an

improvement in overall survival of 3.6 months (14.9 months with radium-223 and 11.3 months with placebo) [24] illustrating a benefit to radium-223 even in the second-line setting. For this reason, the authors typically reserve radium-223 for use in the second- or third-line mCRPC setting in men with bone-only symptomatic disease.

Considerations

The combination of agents or addition of one agent after progression on another is also an active area of research. The best choice for the second-line therapy will mostly depend on the previous therapy given (Fig. 1). If chemotherapy has not been given and the patient has a good performance status with no significant contraindications to chemotherapy, that is likely the best choice for second-line therapy. Consideration can also be given to immunotherapy and radiopharmaceutical therapy in the appropriate clinical setting. The benefit to sequential novel androgen-directed therapy is not yet clear but could also be considered based on patient characteristics or biomarker analyses.

Third-line therapy and beyond

Chemotherapy

Cabazitaxel seems to maintain some clinical activity even if given in the third-line setting. In the largest retrospective review of 254 men treated with novel agents in the third- and fourth-line settings, cabazitaxel and enzalutamide seemed to have the best activity with objective response rates of 12–16 % and PSA response rates 25–28 % [44]. A retrospective review of 79 men who had progressed after docetaxel and abiraterone showed an overall survival of 10.9 months, progression-free survival of 4.4 months, along with 35 % of patients having >50 % PSA responses when treated with cabazitaxel [45]. Another retrospective study of third-line cabazitaxel or enzalutamide in 173 men showed a trend toward a greater PSA decline with cabazitaxel, with 35.9 % of men achieving a PSA decline of >50 % compared to 27.9 % of men receiving enzalutamide [46]. Another smaller study of 89 men treated with cabazitaxel in the third-line setting (all previously treated with docetaxel and abiraterone acetate) showed a PSA response rate >50 % in 49 % of men and partial radiographic response by RECIST imaging criteria in 20 % of the men with measurable disease (35 men) [47].

Novel androgen-directed agents

There is only preliminary data about the activity of abiraterone and enzalutamide in the third-line setting. Most of these retrospective reviews included patients treated with one line of chemotherapy and one of the novel androgen-directed therapies.

A prospective, open label study of abiraterone in 36 men who had progressive disease after at least 3 prior lines of therapy showed a decrease in PSA levels of >50 % in 22 of the 36 patients (61 %) with 7 of the 12 patients with measurable disease showing radiographic response [48] suggesting that there is some clinical activity with abiraterone in later lines of therapy.

Enzalutamide in the third-line setting was explored in a retrospective review of 137 men previously treated with docetaxel and abiraterone and showed a PSA response rate of >50 % in 18 % of men and PSA response rate of >30 % in 38 % of

men with a median overall survival of 8.3 months [49]. In a review of 63 men being treated with enzalutamide in the third-line setting, 29 % of men had a PSA decline of >50 % and 21 % had stable disease [50].

Compared to enzalutamide in the second-line setting, a retrospective review of 115 men who received enzalutamide in the second- or third-line (n = 47 men in second line; n = 68 men in third line) setting showed that there was no difference in PSA response rate, time to progression, or overall survival. However, the response rates were poor in both groups (22 and 26 %), and overall survival was relatively low in both groups treated (10.6 and 8.6 months) [42]. Another review of 75 men treated with enzalutamide in the third-line setting showed a median time to disease progression of 15.9 weeks, which suggests decreased effectiveness in this later line of therapy when compared to data from the AFFIRM trial (second-line enzalutamide) where the median time to disease progression was about 36 weeks [51].

A comparison of both novel androgen-directed agents compared to cabazitaxel was done in a retrospective review of 260 patients who received abiraterone, cabazitaxel, or enzalutamide in the third-line setting and showed no significant differences in the progression-free survival (4 months) or overall survival (11 months) based on which agent was used in the third-line setting [52].

Considerations

Although the evidence is weak, the authors recommend a consideration of cabazitaxel as a third-line therapy for patients who are chemofit and have previously received docetaxel as well as at least one prior androgen-directed agent (Fig. 1). Alternatively, in men with symptomatic bone-predominant disease, radium-223 is a good option for patients who have not received this agent. Finally, abiraterone or enzalutamide are the least preferred option in the third-line setting unless the patient has not received either agent previously. In addition, our preference is to alternate taxane therapies with androgen-directed therapies in an effort to minimize cross-resistance, although this hypothesis remains to be proven.

Biomarkers to predict who will respond to therapy

While there have been a number of proposed biomarkers for determining prognosis in patients with mCRPC, few exist to help decide on treatment selection [53].

Androgen-receptor splice variant 7 (AR-V7) was the first biomarker to be potentially useful in this arena when it was shown to predict poor response to enzalutamide or abiraterone in a pilot study. Sixty-two men (half treated with abiraterone and half with enzalutamide) were studied. Thirty-nine percent of enzalutamide-treated and 19 % of abiraterone-treated patients had detectable AR-V7 splice variant in circulating tumor cells. Those with the splice variant (AR-V7 positive) showed poor response to both agents (0 % PSA response) in comparison to those without the splice variant (AR-V7 negative), where 53 % receiving enzalutamide had a PSA response and 68 % receiving abiraterone had a response [54••]. A follow-up study showed that with 202 patients in the first-line setting, those who were AR-V7 positive only had a 27 % PSA response rate to novel androgen-directed agents compared to a 66 % PSA response rate to novel anti-androgens in those who were AR-V7 negative [55]. In the second-line setting, PSA response to novel androgen-directed agents was poorer with only

5 % of AR-V7-positive men responding compared to 27 % of men without detectable AR-V7 splice variant (AR-V7 negative) [55].

This does not seem to be true for taxane-based chemotherapy [56, 57]. In one study, of the 37 patients treated with taxane chemotherapy, 17 were AR-V7 positive and of those, 41 % had a PSA response to taxane chemotherapy compared to a 65 % PSA response rate in the AR-V7-negative group (non-significant difference of $p = 0.19$) [56]. Another study of 29 patients with detectable circulating tumor cells, 16 of whom were AR-V7 positive, showed no difference in progression-free survival between those with and without detectable AR-V7 splice variant when treated with cabazitaxel [57].

Another single-institution study of 161 patients showed that the prevalence of AR-V7 positivity increases as the disease progresses with more lines of therapy [58]. Furthermore, patients who tested positive for AR-V7 splice variant had 2.3 months greater median survival (8.9 versus 4.6 months) when treated with taxane chemotherapy compared to novel anti-androgen therapy [58]. It is important to note that this study suggests that AR-targeting therapy was equivalent to taxane therapy in AR-V7-negative patients, while taxane therapy appeared superior to androgen-targeting therapy in the AR-V7-positive patients [58]. Taken together [57–59], it is reasonable to test patients, especially after progression of disease on initial mCRPC therapy, and if an AR-V7-positive result is obtained, taxane chemotherapy over a novel anti-androgen should be considered (Fig. 1). These findings await prospective validation, and it should be noted that widespread AR-V7 testing is not currently available in most settings.

Another promising biomarker for mCRPC pertains to the presence or absence of DNA damage repair mutations, either at the germline level, somatic level, or both. In additional to somatic (i.e., tumor-specific) mutations, germline DNA testing of patients and tumors is becoming more relevant. Recently, a study of 692 men with metastatic prostate cancer, irrespective of family history or age of onset, performed germline testing for 20 cancer-susceptibility mutations and found that 11.8 % of men had germline DNA repair gene mutations and this did not differ based on presence or absence of family history [60••]. A separate study was done in 49 men with mCRPC treated with olaparib—a poly ADP ribose polymerase (PARP) inhibitor important in inducing synthetic lethality in tumors with pre-existing DNA repair defects—and showed that 16 of 49 evaluable patients had a favorable response to olaparib and 88 % of those who responded had inactivating germline or somatic mutations in DNA repair genes, especially in the homologous recombination pathway (*BRCA1*, *BRCA2*, *ATM*) [61••]. In addition, preliminary data suggest that men with tumors who harbor DNA damage repair defects may be more sensitive to platinum-based chemotherapies (that are otherwise not widely used in mCRPC). Based on the higher than expected prevalence of (germline and somatic) DNA repair mutations in metastatic CRPC, a number of trials are currently testing the use of investigational PARP inhibitors or platinum chemotherapy agents in these patients [62].

Conclusion

Metastatic prostate cancer is a global disease of critical importance given its high prevalence. There are currently many treatment options and many others yet in

development. Optimal treatment sequencing in mCRPC (Fig. 1) will depend on the individual patient characteristics and may also include other factors such as age, cost of therapy, and clinical trial availability. In addition, there are some promising biomarkers that could help guide treatment decision-making. Further research will be needed to better inform therapy choice for men with mCRPC and many such trials are ongoing (Table 1). With so many life-prolonging therapies at our fingertips, the challenge of the next 5 to 10 years is to learn how to best combine and sequence all of these agents in an evidence-based manner and with additional consideration of biomarker data that will further help to refine treatment selection.

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Compliance with ethical standards

Conflict of interest

Catherine E. Handy declares that she has no conflict of interest.

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Human and animal rights and informed consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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