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Pharmacotherapeutic Management of Metastatic, Castration-Resistant Prostate Cancer in the Elderly: Focus on Non-Chemotherapy Agents

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Abstract

In the past 4 years, five new agents have been approved for metastatic, castration-resistant prostate cancer. Four of them are non-chemotherapeutic and generally well tolerated. However, each has toxicities that can negatively impact patients, particularly the elderly. This review covers the epidemiology of prostate cancer in elderly men. It discusses the efficacy data for sipuleucel-T, abiraterone in chemotherapy-naïve patients, enzalutamide in chemotherapy-naïve patients and radium-223 and presents any additional studies done for those over 75 years of age. Disease burden, such as the presence or absence of visceral disease, and comorbid conditions weigh into the selection of therapy and are discussed here. Drug–drug interactions between these agents and other drugs commonly used in the elderly population are also considered. The emerging therapies tasquinimod and ipilimumab are reviewed. With the arrival of so many agents for prostate cancer, selection of the most appropriate agent can be perplexing, particularly because these agents were tested against placebo, not one another. Furthermore, the study population differs significantly from those seen in clinical practice. This review addresses these issues.

1 Background

Just 5 years ago, effective treatment options for men with metastatic, castration resistant prostate cancer (mCRPC) were limited to chemotherapy. Clinicians could try secondline hormone therapy with incomplete androgen receptor antagonists (bicalutamide, nilutamide, flutamide), non-specific inhibition of cytochrome P450 enzymes (ketoconazole), steroids and estrogens. However, while these agents occasionally reduced tumor burden and cancer-related symptoms, there were no robust data supporting their use, and they did not significantly prolong survival. Chemotherapy with docetaxel combined with prednisone

modestly improved survival and reduced cancer-related pain relative to mitoxantrone with prednisone, but treatment was associated with significant adverse events [1, 2].

In the past 4 years, four non-chemotherapeutic agents have been approved for mCRPC based on improved survival in randomized, phase III studies. A fifth agent, cabazitaxel, is a chemotherapeutic agent that has been shown to prolong survival after docetaxel chemotherapy [3]. This agent can lead to significant neutropenia and fatigue, which may limit its applicability to the elderly. This review focuses on non-chemotherapy agents, which are described within.

2 Epidemiology

In 2014, an estimated 233,000 people will be diagnosed with prostate cancer, and 29,480 will die of prostate cancer in the US alone [4]. The probability of developing prostate cancer in men over 70 years is 11.2 %. For men 80 years, an estimated 84,636 will die of cancer with 15,188 (18 %) of those deaths attributable to prostate cancer [4]. In Europe, 70,000 men are predicted to die of prostate cancer in 2014 [5].

Recent analyses have found that men diagnosed with prostate cancer at or over the age of 75 years have a particularly poor prognosis. For example, the men are more likely to have high-grade disease (23–30 %) and more likely to have metastatic disease at diagnosis than their younger counterparts [6]. Men 75 years represent a quarter of all men diagnosed with prostate cancer and nearly half of all men diagnosed with metastatic disease. Additionally, 53 % of prostate cancer-related deaths occur in men 75 years.

3 Sipuleucel-T

3.1 Sipuleucel-T Efficacy and Safety

In 2010, the US FDA approved sipuleucel-T (Provenge) for asymptomatic or minimally symptomatic mCRPC [7]. To date, it is the only immunological therapy for prostate cancer approved in the US and European Union (EU) [7, 8]. Sipuleucel-T is an adoptive cellular immunotherapy designed to activate an immune response directed against prostatic acid phosphatase (PAP) [7, 9–11]. The treatment production process involves leukapheresis for removal of the white blood cells, which are sent to a facility where the patient's peripheral blood mononuclear cells are exposed to a prostatic acid phosphatase-granulocyte macrophage colony-stimulating factor (PAP-GM-CSF) fusion protein ex vivo and then re-infused into the patient. This process is repeated three times, and thus requires good vascular access. The IMPACT (Immunotherapy for Prostate Adenocarcinoma Treatment) study randomized 512 subjects in a 2:1 fashion to sipuleucel-T ($N = 341$) or placebo ($N = 171$) [12]. It showed a significant decrease in death from prostate cancer in those men who received sipuleucel-T (hazard ratio [HR] 0.77; 95 % confidence interval [CI] 0.61–0.98; $p = 0.04$). The median survival was 25.8 months for the sipuleucel-T group versus 21.7 months for the placebo group. The median age on this study was 71 years (range 40–91 years). A post hoc analysis comparing men aged >71 years with those 71 years suggested that the benefit of sipuleucel-T was at least as good in the older subset as in the younger one [12]. There was not a significant decrease in prostate specific antigen (PSA), tumor size or

symptoms. Therefore, it should not be used in patients who require narcotic medications for prostate cancer pain or those who have rapidly growing tumors. The adverse events between the placebo arm and the sipuleucel-T arm were similar, except for those adverse events related to cytokine release, namely chills, fever, headache and flu-like symptoms, which were reported at least twice as often in the sipuleucel-T arm than in the placebo arm. There were no anaphylactic reactions nor were there autoimmune diseases. The grade 3–5 adverse events were similar between the sipuleucel-T arm and placebo arm. Most subjects completed all three treatments, and there are no described treatment discontinuations or treatment-related deaths in the IMPACT study.

Investigators used an on-going phase IV registry to examine elderly patients' anticancer response to sipuleucel-T [13]. As of May 2013, there were 278 of 1,254 (20 %) in the registry who were aged ≥ 80 years old. The analysis compared those aged <80 years (median age 69 years) with those aged ≥ 80 years old (median age 83 years). It found that those aged ≥ 80 years old were more likely to have cancer-related symptoms (30 vs 47.2 % of patients) and less likely to have Gleason ≥ 8 cancer at diagnosis (60.3 vs 49.6 %). The mononuclear cell product was similar between the two groups, suggesting that older age does not negatively impact the product parameters thought to be important for immunogenicity.

3.2 Sipuleucel-T Drug Interactions

There are no drug interactions described for sipuleucel-T.

4 Abiraterone

Abiraterone (Zytiga) is a P-450c17 inhibitor that interferes with androgen production through inhibition of two key enzymatic steps (17 hydroxylase and 17,20 lyase enzymes) [14]. Whereas surgical castration and chemical castration with luteinizing hormone-releasing hormone (LHRH) agonists and antagonists block testosterone production by the testicles, abiraterone can block production by the testicles, adrenal glands and tumors themselves. Abiraterone currently has approval for use in several countries, including the US and EU [8, 9], for men with mCRPC either before chemotherapy or after chemotherapy. Since this review focuses on interventions prior to chemotherapy, we will focus on efficacy in that population.

4.1 Abiraterone Efficacy and Safety

A phase III, double-blind study of 1,088 subjects randomized 1:1 to abiraterone 1,000 mg daily plus prednisone 5 mg twice daily ($N = 546$) versus placebo plus prednisone 5 mg twice daily ($N = 542$) showed a 25 % decreased risk of death in those treated with abiraterone (HR 0.75; 95 % CI 0.61–0.93; $p = 0.01$) [15]. This study was halted and patients unblinded after an interim analysis showed that the study had met the co-primary endpoint, radiographic progression-free survival (PFS). Although it did not meet the study's requirement for statistical significance for overall survival ($p = 0.001$), it did trend toward it. Median overall survival was calculated after 333 deaths (47 % of 773 events). It was not reached in the abiraterone group and was 27.2 months (95 % CI 26.0 to not reached) in the placebo group. The median age on the abiraterone plus prednisone arm was 71.0 years versus 70.0 years on

the prednisone alone arm. There were 185 patients (34 %) aged ≥ 75 years in the abiraterone plus prednisone arm and 165 (30 %) in the prednisone alone arm. Subgroup analysis suggests that the aged ≥ 75 years group benefited from abiraterone plus prednisone in terms of radiographic PFS HR 0.64 (95 % CI 0.48–0.84) and overall survival 0.71 (0.51–1.00).

The abiraterone + prednisone arm had more cardiac adverse events, which were defined as ischemic heart disease, myocardial infarction, supraventricular tachyarrhythmia, ventricular tachyarrhythmia, cardiac failure and possible arrhythmia-related investigations, signs and symptoms [15]. On the abiraterone + prednisone arm, 102 patients (19 %) had a cardiac adverse event versus 84 (16 %) on the placebo + prednisone arm. Of those, 31 (6 %) were grade 3 or 4 versus 18 (3 %), respectively. Cardiac failure led to five treatment discontinuations and two fatalities in the abiraterone arm whereas no treatment discontinuations and one fatality occurred in the placebo group. These events may be related to hypertension, which was also more prevalent in the abiraterone arm. The clinical trials excluded patients with New York Heart Association Class II–IV heart disease or left ventricular ejection fraction <50 %. Patients with significant heart failure or symptomatic heart failure should be treated with caution or possibly not at all with abiraterone [16].

Those subjects who received abiraterone were also more likely to have adverse events related to the liver, namely elevation in transaminases [15]. In the abiraterone + prednisone arm, 63 patients (12 %) had an elevated alanine aminotransferase (ALT) versus 27 (5 %) on prednisone alone, and 58 (11 %) had aspartate transaminase (AST) elevations versus 26 (5 %), respectively. No patients on the clinical trials experienced liver failure. Liver function tests (ALT, AST, bilirubin) should be checked every 2 weeks for the first 3 months and monthly thereafter. Treatment should be interrupted for AST or ALT >5 times the upper limit of normal or bilirubin >3 times the upper limit of normal and restarted once the AST and ALT is under 2.5 times the upper limit of normal and bilirubin is under 1.5 times the upper limit of normal [18]. The liver function should be monitored more closely in patients with baseline moderate hepatic dysfunction. It is likely that the liver and cardiac issues are ‘treatment related’ since they occurred more frequently in the abiraterone + prednisone arm, but it is not possible to know for sure. There were more treatment discontinuations in the abiraterone + prednisone arm (19 %) than in the prednisone arm (12 %). This study does not report on whether the difference is statistically significant.

Abiraterone should be taken while fasting because it has variable absorption with high-fat foods [16].

4.2 Controversies Regarding Steroids with Abiraterone

Inhibition of P-450c17 leads to excess mineralocorticoids. Attard et al. [14] described the endocrine effects of abiraterone 1,000 mg daily given to 42 men with CRPC without concomitant steroids. In that study, subjects experienced typical signs of mineralocorticoid excess (i.e., hypertension, hypokalemia and fluid overload). They received the selective mineralocorticoid receptor antagonist eplerenone 50–200 mg/day, which abrogated those adverse events in 38 of 42 patients. Three patients required dexamethasone 0.5 mg/day in addition to eplerenone. This study also confirmed profound suppression of androgen

production, which is the intended function, as well as decreased glucocorticoids, which is an unintentional consequence.

Clearly P-450c17 inhibition with abiraterone deranges innate steroid production, frequently causing significant symptoms or electrolyte disturbances for patients, and the addition of exogenous steroids ameliorates this. Dexamethasone 0.5 mg/day appears to be sufficient to inhibit excess mineralocorticoid production and replace glucocorticoids [17–19], yet the accepted regimen [16] uses prednisone 5 mg twice daily, which is biologically equivalent to three times the dose of dexamethasone. Prednisone at this dose can cause symptoms of glucocorticoid excess. The package insert for abiraterone [16] describes some adverse events related to glucocorticoid excess: hyperglycemia (56.6 % in the abiraterone + prednisone arm vs 50.9 % in the placebo + prednisone arm), hypertriglyceridemia (62.5 vs 53 %, respectively) and confusion (13.3 vs 9.1 %). The dose of prednisone at 5 mg twice daily was likely chosen in part because it also has anti-cancer effects [20], but it is not clear that, when added to abiraterone, prednisone contributes to the anti-tumor activity. Therefore, if patients experience prednisone-related adverse events, we believe it is reasonable to decrease the amount of prednisone to 3–5 mg per day. At this dose, the mineralocorticoid excess and glucocorticoid deficiency should be well controlled. Importantly, this dose has not been tested in a randomized clinical study, and it is possible that decreasing the prednisone would decrease the efficacy of abiraterone/prednisone.

4.3 Abiraterone Drug Interactions

There are significant interactions between abiraterone and numerous drugs [16], but the following are most germane to the geriatric population. Abiraterone potently inhibits CYP2D6. When abiraterone is coadministered with a CYP2D6 substrate, the combination leads to increased exposure to the substrate. Examples of these include amiodarone, carvedilol, donepezil, fentanyl, flecainide, fluoxetine, haloperidol, hydrocodone, metoprolol, paroxetine, propranolol, tamsulosin, tramadol, vardenafil and venlafaxine. St John's Wort and carbamazepine are CYP3A4 inducers that can lead to decreased exposure to abiraterone. Of note, increased exposure to fluoxetine can lead to a prolonged QT interval.

Most of these drugs listed here are antidepressants, pain medications, and cardiac medications. Increased exposure to them in any population can lead to adverse events, but they may be even more pronounced in the elderly population [21]. Care must be taken in patients taking these drugs.

5 Enzalutamide

5.1 Enzalutamide Efficacy and Safety

Enzalutamide (Xtandi) is a pure androgen receptor antagonist that has approval for use prior to and after chemotherapy in patients with mCRPC in the US and EU [8, 9]. For this review, we will focus on efficacy in the chemotherapy-naïve group. The PREVAIL study randomized 1,717 patients to enzalutamide 160 mg orally per day ($N = 872$) or placebo ($N = 845$) in a blinded fashion [22]. It decreased the hazards of death by 29 % (HR 0.71, 95 % CI 0.60–0.84; $p < 0.0001$) and reduced the risk of radiographic progression by 81 % (HR 0.186, 95 % CI 0.15–0.23; $p < 0.0001$). Quality of life was measured by the FACT-P (Functional

Assessment of Cancer Therapy–Prostate) questionnaire. This study showed that enzalutamide was able to increase the time to quality-of-life deterioration to 11.3 months with enzalutamide versus 5.6 months with placebo (HR 0.625; $p < 0.0001$). Improvements across a range of quality-of-life domains have also been reported, but detailed information is not available yet [23].

In the phase I/II study of enzalutamide, fatigue and seizures were observed at higher doses and fatigue was the dose-limiting toxicity [24]. Based on this information, a dose of 160 mg per day was used in the phase III clinical trials [22, 25]. Subjects included in these studies could not have brain or leptomeningeal metastases, history of seizure, transient ischemic attack or loss of consciousness within 12 months, or any condition that may predispose to seizure. With appropriate patient selection (as above) and the dose selected for phase III trials, seizures proved uncommon. In the PREVAIL study, two subjects experienced a seizure, one in the placebo group and another in the enzalutamide group [22]. Further investigation revealed that each subject had a seizure history that was not reported to the investigators at the time of enrollment.

Other adverse events from the PREVAIL study [22] that were more common in the enzalutamide group versus placebo were hypertension (13 vs 4 %), fatigue (36 vs 26 %), back pain (27 vs 22 %), constipation (22 vs 17 %) and arthralgia (20 vs 16 %). Falls were more common in the enzalutamide group as well (12 vs 5 %). Grade 3 hypertension was more common in the enzalutamide group (7 vs 2 %). Cardiac events were similar between the two groups. Despite these toxicities, enzalutamide was generally well tolerated. Six percent of patients in the enzalutamide group discontinued treatment because of adverse events, and 6 % on the placebo group discontinued. Although not included in the original PREVAIL publication, the package insert reports that non-pathologic falls occurred in 8.8 % in the enzalutamide group and 3.0 % in the placebo group [26].

Importantly, enzalutamide does not require co-administration with a steroid.

Data specific to the elderly who participated in PREVAIL are not currently available. However, an analysis of AFFIRM [25], the study of enzalutamide versus placebo in patients previously treated with chemotherapy, has been published [27]. In men ≥ 75 years, all efficacy measures were improved in the enzalutamide group versus placebo. Overall survival in the enzalutamide arm was 18.2 versus 13.3 months in the placebo arm (HR 0.61; 95 % CI 0.43–0.86). Radiographic PFS, time to PSA progression and time to PSA response were also significantly improved in the enzalutamide group. Adverse events among those who received enzalutamide were similar between men < 75 years and men ≥ 75 years except for edema (22.1 vs 12.5 %), fatigue (39.7 vs 31.6 %) and diarrhea (26.6 vs 19.6 %), which were higher in the older group. Statistical significance was not reported, but the authors described these differences as ‘major’. Three people < 75 years and two people ≥ 75 years had seizures.

5.2 Enzalutamide Drug Interactions

Enzalutamide is a strong CYP3A4 inducer [26]. When enzalutamide is coadministered with a CYP3A4 substrate, it has the potential to decrease exposure to that substrate. Examples of

this include amiodarone, amlodipine, diclofenac, fentanyl, hydrocodone, nifedipine, warfarin. St John's wort, a strong CYP3A4 inducer, may decrease exposure to enzalutamide.

Of note, enzalutamide also interferes with the metabolism of multiple antiepileptic medications. However, patients with a history of seizures should not be on enzalutamide, as it may lower the seizure threshold [26].

6 Radium-223

Radiopharmaceuticals have been used to treat painful prostate cancer bone metastases for decades [28]. The first radiopharmaceuticals (strontium-89 and samarium-153) emitted beta particles. Although their use decreased pain in up to 80 % of patients [28], a survival or progression-free survival benefit has not been demonstrated. The concern about beta particles is that they can travel to the bone marrow and cause myelosuppression. Rates of thrombocytopenia in clinical trials were as high as 94 %, and rates of leukopenia reached 92 %. Hemoglobin <8 g/dL occurred in approximately 8.5 % of patients. Leukopenia <500/mm³ occurred in approximately 12 % of patients. Thrombocytopenia with platelets <50,000/mm³ occurred in 6–33 % of patients [28]. Strontium, in particular, was reserved until after chemotherapy because of the concern that cytopenias would prohibit the use of palliative chemotherapy [29]. Alpha particles are much larger and heavier than beta particles and as a result carry more energy and do not travel as far [30]. Therefore, it was hypothesized that they would cause more DNA double-strand breaks, which are more likely lethal to cancer cells than single strand breaks, and that they would cause less myelosuppression.

6.1 Radium-223 Efficacy and Safety

In 2013, the first alpha-emitter, radium-223 (Xofigo), was approved in the US and EU [8, 9] for men with mCRPC with symptomatic bone metastases and no visceral metastatic disease. The ALSYMCA (Alpharadin in Symptomatic Prostate Cancer) study randomized 921 subjects 2:1 to radium-223 ($N = 614$) or placebo ($N = 307$) [31]. Radium-223 50 kBq/kg was administered every 4 weeks for six doses. Patients with visceral disease or lymph nodes >3 cm were excluded from this study because radium-223, a calcium mimetic, is taken up by the bone and not other cancer sites. The subjects included in this study had either received chemotherapy or were considered unfit for chemotherapy. The median survival in the radium-223 group was 14.9 versus 11.3 months in the placebo group (HR 0.70; 95 % CI 0.58–0.83; $p < 0.001$). The study was terminated early given the observed efficacy. Palliative benefits were not formally and prospectively examined using validated patient-reported instruments; however, radium-223 led to improvement in pain as measured by 'bone pain' as an adverse event and as implied by time to opiate medication use. Fifty percent of radium-223 subjects reported bone pain compared with 62 % of placebo patients. The use of external beam radiation therapy and opiate pain medications were reduced by 33 and 38 %, respectively, in those on radium-223. Subjects in the radium-223 group reported reduction in pain at week 16 ($p < 0.001$), which lasted until week 24 ($p = 0.001$) [32]. Finally, time to first symptomatic skeletal event (defined as a symptomatic bone fracture, receiving palliative external beam radiotherapy [EBRT], spinal cord compression, or orthopedic intervention) was longer in the radium-223 group: 15.6 versus 9.8 months (HR 0.66; 95 % CI 0.52–0.83).

In the ALSYMPCA trial, hematologic events overall were similar between the two groups [31]. However, grade 3–4 neutropenia was higher in the radium-223-treated group (3 vs 1 %). One subject in each group experienced neutropenic fever as a result. Grade 3–4 thrombocytopenia occurred in 6 % of the radium-223 group versus 2–3 % of placebo. One subject in the radium-223 group died as a result of thrombocytopenia. Non-hematologic toxicities that occurred more often in the radium-223 group were rare, though diarrhea occurred more in the radium-223 group (25 vs 15 %)—likely related to the gastrointestinal route of radium excretion. Some patients experienced a flare in their bone pain after the first dose. There were no significant differences between the radium-223 and placebo groups in terms of clinically meaningful adverse events. Furthermore, more patients in the placebo arm discontinued the study than those in the radium-223 arm.

The ALSYMPCA trial included 261 men over the age of 75 years. There were 171 (28 %) in the radium group and 90 (29 %) in the placebo group. A post hoc analysis of ALSYMPCA examined men by age: <67, 67–74, and ≥75 years [33]. It found that in the group aged ≥75 years, treatment with radium-223 resulted in statistically significant prolonged overall survival, time to PSA increase and time to increased alkaline phosphatase. There was a trend toward increased time to first skeletal-related event. Furthermore, men in the group aged ≥75 years had similar or fewer adverse events than those in the younger age groups.

Certain precautions need to be made prior to treatment with radium-223 [34]. A complete blood count should be obtained within 1 week prior to each dose. We recommend a platelet count $>100,000/\text{mm}^3$ and leukocyte count $>3,000/\text{mm}^3$ prior to each treatment. The elderly may have decreased bone marrow reserve, but so far there is no guidance as to whether their parameters should be different.

There are no contraindications or precautions with respect to kidney or liver function [34]. There are also no precautions post-treatment, such as a requirement to remain in isolation. Unlike for the beta emitters, there are no precautions for those with urinary incontinence. Treatments are given in an outpatient facility, and then patients are released to go home. Of note, radiopharmaceuticals are not intended for those with impending cord compression, where emergent intervention by neurosurgery and/or radiation oncology is indicated, and patients with impending cord compression were excluded from the ALSYMPCA trial [31].

7 Radium-223 Drug Interactions

There are no known drug interactions with radium-223.

8 Therapies Currently in Clinical Trials

8.1 Tasquinimod

Tasquinimod is an oral agent that inhibits blood vessel formation, but the mechanism of action is incompletely understood [35]. There are not currently any approved therapies in prostate cancer that interfere with angiogenesis, and there have been multiple negative studies with angiogenesis inhibitors tried in prostate cancer [36–38]. A phase II study randomized 201 patients in a 2:1 fashion to tasquinimod 0.25–1 mg/day ($N = 134$) versus placebo ($N = 67$) [39]. Patients were not permitted to have received chemotherapy within 3

years of participating in the study nor could they require narcotics. It found that tasquinimod significantly improved prostate cancer PFS at 6 months: 69 versus 37 % (relative risk 0.49; 95 % CI 0.36–0.67; $p < 0.001$). The median PFS in the tasquinimod group was 7.6 versus 3.3 months for the placebo group ($p = 0.0042$). Participants in the placebo arm were permitted to cross over to the tasquinimod arm at progression, so the trial does not inform about effects on overall or cancer-specific survival. As with sipuleucel-T, there were no significant changes in PSA levels. Interestingly, one fifth of participants were 81 years of age.

Tasquinimod grade 3 or 4 adverse events occurred infrequently [39]. The most common grade 3–4 event was an elevated lipase (5 %) and deep vein thrombosis (4 %). However, many patients in this study had to discontinue treatment prior to progression: 22 % in the tasquinimod arm versus 1 % in the placebo arm. The authors cite grade 1 or 2 toxicities as the chief cause of discontinuation. On-treatment myalgias and arthralgias caused most discontinuations. Importantly, among those >80 years of age, 73 % on tasquinimod required dose reductions versus 50 % of those 80 years. The authors hypothesize this may be related to slower hepatic clearance in the elderly.

As with other angiogenesis inhibitors (such as bevacizumab), caution was exercised in patients with bleeding potential and cardiac disease (recent myocardial infarction, arrhythmias, congestive heart failure). Subjects on warfarin were excluded from the study. Subjects were permitted to join the study if they had no cardiac events in the preceding 12 months. The phase I study of tasquinimod identified asymptomatic elevations in amylase and lipase as adverse events [40]. Although subjects with elevations in pancreatic enzymes had no clinical evidence of pancreatitis, the phase II study excluded those with a history of pancreatitis.

An ongoing phase III study will provide additional information (ClinicalTrials.gov identifier: NCT01234311).

8.2 Ipilimumab

Ipilimumab is an antibody against CTLA-4 that interferes with the cancer's ability to inhibit T cells [41]. In doing this, it also has potential autoimmune consequences such as colitis, rashes, hypo- or hyper-thyroidism, hyperpituitarism, and hypophysitis [42]. Ipilimumab is currently used in metastatic melanoma [34], so oncologists are becoming familiar with the toxicities.

Several studies have examined the efficacy of ipilimumab in mCRPC [43, 44]. A phase I/II study examining several doses of ipilimumab (3, 5 or 10 mg/kg) with or without one 8 Gy dose of external beam radiation (XRT) showed activity in both the chemotherapy-naïve and the chemotherapy-exposed patients [44]. The ipilimumab was given every 3 weeks for four treatments. There were no dose-limiting toxicities at any of the three ipilimumab doses.

In the phase II portion, median age ranged from 65 years in the ipilimumab 10 mg/kg alone group ($N = 16$) to 66 years in the ipilimumab + XRT group ($N = 34$) [44]. In this phase, those who responded or had stable disease received three additional doses of ipilimumab. Approximately 54 % had received prior chemotherapy. The median age varied between

groups but ranged from 57 to 69 years, which is younger than the ages seen in the clinical trials of sipuleucel-T, abiraterone, enzalutamide and radium-223. There were more PSA responses (PSA decline $\geq 50\%$) in the chemotherapy-naïve group than the chemotherapy-exposed group, 26 versus 7 %. There was not a significant difference between the groups that received radiation and the one that did not, but the study was not powered to detect a difference and more patients with chemotherapy exposure were in the XRT group. Treatment-related toxicities in the phase II portion included grade 3 diarrhea that required steroids and/or infliximab in seven patients (14 %); grade 3–4 colitis in eight patients (16 %), all of whom required steroids and/or mycophenolate mofetil; and nine (18 %) had endocrine toxicities, none $\geq$ grade 2. These toxicities are considered immune-related and are of particular interest when studying immune checkpoint inhibitors, such as ipilimumab [42].

The responses in the phase I/II study prompted further exploration in two phase III studies. One study randomized 799 patients who had been treated with chemotherapy in a 1:1 fashion to ipilimumab 10 mg/kg ($N = 399$) versus placebo ($N = 400$). The primary endpoint, overall survival, was not statistically different between the groups (HR 0.85; 95 % CI 0.72–1.00; $p = 0.053$) [45]. There was a difference in PFS favoring ipilimumab (HR 0.70; 95 % CI 0.61–0.82) and PSA response rates ($\geq 50\%$ decline), 13.1 % in ipilimumab versus 5.5 % in placebo. An ongoing study is examining efficacy of ipilimumab in chemotherapy-naïve patients (ClinicalTrials.gov identifier: NCT001057810).

8.3 Other Agents

There are several additional treatments of interest, including ARN509 (androgen receptor antagonist) [46], cabozantinib (cMET and VEGFR2 [vascular endothelial growth factor receptor 2] inhibitor) [47] and PROSTVAC-F/TRI-COM (immunotherapy) [48]. There are several on-going clinical trials examining these agents.

9 Discussion and Future Directions

While the addition of four new non-chemotherapy agents (Table 1) to the oncologist's armamentarium is exciting, it opens up several new questions. First, there is very little guidance about sequencing of these therapies. For instance, the studies of enzalutamide [22] excluded those who had received abiraterone, and vice versa [15]. The efficacy of each of these agents in patients exposed to the other are not known and small retrospective studies [49, 50], as well as preclinical data [51], are suggesting that the activity is less than described in the published phase III trials. It is conceivable that one order might be more beneficial than another. Second, we do not know if combinations of agents will be more effective than sequential administration, but there are several ongoing studies addressing this (Table 2). Third, patient selection for these agents is critical, particularly for treatments that may benefit subsets of patients disproportionately. We have much to learn about the disease in patients treated with multiple therapies. Finally, the performance of these agents in the elderly population merits additional attention. Choosing the correct agent for a patient requires good knowledge of his prostate cancer location and symptoms. For example, enzalutamide would not be appropriate for a patient with metastatic tumor to the brain because of seizure risk. Also, radium-223 monotherapy is inappropriate for patients with significant disease outside of the bones since this agent will not localize to tumors outside of

the bone. The presence or absence of symptoms will help as well. For example, since sipuleucel-T does not lead to rapid decrease of tumor volume, it is inappropriate in a patient experiencing prostate cancer-related pain. Finally, comorbid conditions will steer providers toward one drug or another. Abiraterone may not be appropriate for someone with symptomatic heart failure, and someone with a history of seizure should not be given enzalutamide. Additionally, radium-223 requires good marrow reserve and should not be given to someone with significant myelosuppression.

Although this review focuses on non-chemotherapeutic agents, chemotherapy still holds an important place in the treatment of mCRPC. Docetaxel has been shown to decrease disease burden and symptoms [1, 2]. Furthermore, it has been studied in the elderly and found to be tolerable and effective [52]. Cabazitaxel, which has shown efficacy following docetaxel chemotherapy in mCRPC, has significant toxicities that may limit its use in the elderly [53].

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Key Points

Patients with metastatic, castration-resistant prostate cancer have multiple non-chemotherapeutic options.

Castration-resistant prostate cancer can still respond to androgen-lowering therapies and those targeting the androgen receptor.

While care must be exercised when treating the elderly, there are data to show that these new therapies are well tolerated and prolong survival in this sub-group.

Table 1

Currently available non-chemotherapy agents for metastatic, castration-resistant prostate cancer not previously treated with chemotherapy

Agent	Administration ^a	Special considerations
Abiraterone (Zytiga)/prednisone	Abiraterone 1,000 mg po qday plus prednisone 5 mg po bid	<ul style="list-style-type: none"> • Cardiac toxicity (abiraterone) • Hepatotoxicity (abiraterone) • Steroid derangement (abiraterone) • Adverse events related to glucocorticoid excess (prednisone)
Enzalutamide (Xtandi)	160 mg po qday	<ul style="list-style-type: none"> • Seizures • Falls and pathological fractures
Radium-223 (Xofigo)	50 kBq/kg (1.35 µCi/kg) IV every 4 weeks for 6 doses	<ul style="list-style-type: none"> • Platelet count >100,000/mm³ and leukocyte count >3,000/mm³ prior to each treatment • Not for those with impending cord compression. Only treats bone metastatic disease, not visceral or lymph node disease • Possible pain flare
Sipuleucel-T (Provenge)	Three rounds of leukapheresis and infusions, usually 2 weeks apart	<ul style="list-style-type: none"> • Does not significantly decrease disease burden. Not for people with symptomatic cancer • Venous access required; may need to consider a central line • Not available at all centers

bid twice daily, *IV* intravenous, *po* by mouth, *qday* daily

^aThe doses in the table are those recommended by the US FDA [7]

Table 2

Ongoing trials of metastatic, castration-resistant prostate cancer (mCRPC) including non-chemotherapy agents in combination

Agents	Identifier	Population	Phase
Sipuleucel-T + abiraterone/prednisone	NCT01487863	No visceral disease	II
Sipuleucel-T + enzalutamide	NCT01981122	No visceral disease. No chemotherapy within 2 years of registration. No prior abiraterone, enzalutamide, immune therapy or ketoconazole	II
Ipilimumab + abiraterone/prednisone	NCT01688492	No prior chemotherapy or immunotherapy	I/II
Enzalutamide versus enzalutamide + abiraterone/prednisone	NCT01949337	No prior chemotherapy for mCRPC. No prior abiraterone or enzalutamide	III
Enzalutamide with or without PROSTVAC-F/TRICOM	NCT01867333	No chronically immunosuppressed subjects (e.g., history of splenectomy, stem cell transplant, need for chronic steroids)	II
Radium-223 + abiraterone/prednisone	NCT02097303	Prior chemotherapy for mCRPC permitted. No visceral disease	II

Subjects may not have a contraindication to the agents included in the study nor may they have prior exposure to them