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Treatment of Advanced Prostate Cancer—A Review of Current Therapies and Future Promise

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Despite many recent advances in the therapy for metastatic castration-resistant prostate cancer (mCRPC), the disease remains incurable, although men suffering from this disease are living considerably longer. In this review, we discuss the current treatment options available for this disease, such as taxane-based chemotherapy, the novel hormone therapies abiraterone and enzalutamide, and treatments such as radium-223 and sipuleucel-T. We also highlight the need for ongoing research in this field, because, despite numerous recent advances, the prognosis for mCRPC remains poor. Furthermore, as a growing body of evidence shows the increasing heterogeneity of the disease, and highlights the ongoing need for disease molecular stratification and validation/qualification of predictive biomarkers, we explore this burgeoning research space that is likely to transform how we treat this disease. We describe putative predictive biomarkers, including androgen receptor splice variants, phosphatase and tensin homolog (PTEN) loss, homologous recombination repair defects, including BRCA2 loss, and mismatch repair defects. The development of next-generation sequencing techniques and the routine biopsy of metastatic disease have driven significant advances in our understanding of the genomics of cancer, and are now poised to transform our treatment of this disease.

Despite many recent advances in the therapy for metastatic castration-resistant prostate cancer (mCRPC), the disease remains incurable, although men suffering from this disease are living considerably longer. In this review, we discuss the current treatment options available and highlight the need for ongoing research in this field.

Standard treatment for mCRPC, with androgen deprivation by either orchiectomy or luteinizing hormone-releasing hormone (LHRH) therapy, remains effective in improving both disease prognosis and symptoms (Lorente et al. 2015). However, suppressing testosterone offers disease control for only an average of 18 to 36 months before the disease enters the castration-resistant phase (Petrylak et al. 2004; Lam et al. 2006). Once the disease is no longer castration sensitive, further treatment is needed, with the aim of increasing overall survival (OS) and, perhaps more importantly, improving symptoms and promoting quality of life. In this review, we discuss the current treatment options available for patients with advanced disease, and explore the relative advantages and disadvantages of approved treatments, including chemothera-

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py, novel hormone therapies such as abiraterone and enzalutamide, as well as radium-223 and sipuleucel-T. We also highlight the need for ongoing research in this field, because, despite these numerous recent advances, the prognosis for mCRPC remains poor. Furthermore, as a growing body of evidence shows the increasing interpatient heterogeneity of the disease (Robinson et al. 2015), we explore the increasing need for disease molecular stratification, describing putative predictive biomarkers, including androgen receptor splice variants (AR-SVs), phosphatase and tensin homolog (PTEN) loss, and homologous recombination (HR) repair defects, including BRCA2 loss and mismatch repair (MMR) defects.

CURRENTLY AVAILABLE TREATMENT OPTIONS

Here, we discuss the currently available treatment options for advanced disease. At the time of writing, no preferred sequence of treatment has been established (Fitzpatrick and de Wit 2014). Treatment decisions should be made by the patient's treating clinician, in conjunction with the patient and their family, as well as with the input of a multidisciplinary team. It also depends substantially on patient preference, current symptoms, and burden of disease, as well as local availability. With all treatments, patients should be monitored closely for evidence of clinical, biochemical, and radiological progression (biochemical monitoring alone is inadequate). If the patient is not participating in a clinical trial, these can be performed at the physician's discretion. However, baseline scans and repeat imaging every 3–6 months are highly recommended (Scher et al. 2016) because a major challenge remains in determining the optimal timing of treatment switch decisions.

Chemotherapy

Docetaxel

Docetaxel chemotherapy was the first treatment to show an improvement in OS in mCRPC following two landmark phase III trials. These trials showed improvement in OS, symptoms, prostate-specific antigen (PSA), and quality of life of mCRPC patients treated with docetaxel and prednisolone versus mitoxantrone and prednisolone (Tannock et al. 2004; Berthold et al. 2008). This survival benefit was seen across all age groups, and, following these studies, an established regimen of three weekly intravenous docetaxel for 10 cycles is given as first-line chemotherapy.

Taxanes exert their anticancer activity by targeting microtubules during mitosis and interphase, and causing stabilization of the mitotic spindle leading to arrest of mitosis and cell proliferation, ultimately causing cell death (Azarenko et al. 2014). The mechanism of action is not fully understood; taxanes are also thought to have some antiandrogenic properties, potentially being able to block nuclear translocation of the androgen receptor (AR), which is also microtubule dependent (Gan et al. 2009; Zhu and Kyprianou 2010; Darshan et al. 2011; van Soest et al. 2013; Fitzpatrick and de Wit 2014). A phase III trial performed in 2003, TAX327, confirmed that a PSA decline of $\geq$50% occurred in 45% of patients treated with docetaxel with prednisolone with a median OS of 19.2 months (Berthold et al. 2008). The benefits of prednisone/prednisolone in this regimen remain, however, controversial and there are increasing concerns about iatrogenic steroids being able to drive disease resistance.

Docetaxel is administered intravenously every 3 weeks for a recommended 10 cycles (Seruga and Tannock 2011), although again the optimal treatment duration is not well defined and merits further evaluation. This is usually at a dose of 75 mg/m^2, although dose reductions can be introduced depending on tolerability. Side effects experienced are similar to those seen with many other types of chemotherapy, including nausea, vomiting, and cytopenias, with some patients experiencing subsequent neutropenic sepsis. Docetaxel (Sanofi-Aventis) use is also associated with both motor and sensory peripheral neuropathy, which can develop with cumulative doses. Retreatment with docetaxel, especially in patients whose tumors have never been determined to be refractory to this agent bears further evaluation for men with dis-

ease recurrence, especially if more than 6 months of remission have elapsed since previous docetaxel exposure. With docetaxel now being used also for treatment-naïve metastatic disease at diagnosis, retreatment for progressing mCRPC also needs further evaluation and may still lead to patient benefit.

Cabaxitaxel

The other approved chemotherapy for treatment of mCRPC is the semisynthetic taxane, cabazitaxel, which exerts a similar mechanism of action, causing cell death by disruption of microtubule function (Vrignaud et al. 2014). Cabazitaxel was selected to overcome the emergence of taxane resistance and has been shown to have antitumor activity in both the postdocetaxel and chemotherapy-naïve setting and to exert antitumor activity in docetaxel-resistant cancers (Pivot et al. 2008). Following the results of the phase III TROPIC trial, this drug was granted approval by the Food and Drug Administration (FDA) in 2010, as a second-line treatment following docetaxel. This trial confirmed important efficacy activity of cabazitaxel with a survival advantage when combined with prednisolone compared to the drug mitoxantrone with prednisolone (de Bono et al. 2010).

Two further phase III studies have confirmed the efficacy of cabazitaxel, including FIRSTANA, which examined whether cabazitaxel at two doses (20 mg/m^2 or 25 mg/m^2) was superior to docetaxel 75 mg/m^2 in terms of OS in chemotherapy-naïve mCRPC patients. This FDA-mandated trial was the first study in CRPC to compare two life-prolonging therapies (Tannock et al. 2004; de Bono et al. 2010), and did not show superiority for OS of cabazitaxel (20 mg/m^2 or 25 mg/m^2) versus docetaxel in the 1178 patients treated. Progression-free survival and PSA response did not differ significantly across treatment arms, although tumor responses were significantly higher for cabazitaxel 25 mg/m^2 versus docetaxel (Sartor 2016). In this trial, cabazitaxel at 20 mg/m^2 was best tolerated. The PROSELICA study was a phase III noninferiority study of cabazitaxel 20 mg/m^2 versus cabazitaxel 25 mg/m^2 in 1200 mCRPC patients who had all been previously treated with docetaxel (de Bono 2016). The results from this FDA-mandated trial confirmed the previously reported antitumor activity of cabazitaxel in patients previously treated with docetaxel. The trial also met the predefined noninferiority end point, indicating that a reduced dose of 20 mg/m^2 of cabazitaxel maintained at least 50% of the OS benefit of 25 mg/m^2.

Cabazitaxel is administered similarly to docetaxel, via an intravenous infusion given once every 3 weeks. Based on the above trials, the standard dose remains 25 mg/m^2, and this higher dose does appear more active. However, this can now be confidently reduced to 20 mg/m^2 in selected patients, for example, those with a decreased performance status or who experience toxicity such as neutropenic sepsis or are unable to tolerate the side-effect profile. Side effects experienced for cabazitaxel are similar to those with docetaxel, and most commonly include neutropenia, nausea, fatigue, and diarrhea (Heidenreich et al. 2013; Wissing et al. 2013a; Bracarda et al. 2014). Concomitant steroids and antiemetics are given prophylactically to minimize side effects. Chemotherapy-induced peripheral neuropathy is much less common with cabazitaxel, with symptoms ranging from numbness in the peripheries and cold insensitivity to pain and loss of balance. The current recommendation is also for up to 10 cycles of cabazitaxel to be administered, provided the patient is tolerating the treatment well and does not show evidence of clinical, biochemical, or radiological progression (Galsky et al. 2010), although the optimal duration of treatment with this agent remains poorly defined.

Mitoxantrone

The FDA initially approved mitoxantrone in 1996 for palliative treatment in mCRPC when a small phase III trial showed some antitumor activity and symptomatic relief, but without significant survival benefit in unselected patients (Tannock et al. 1996). Retrospective analyses of data from phase III randomized controlled trials, including mitoxantrone in a treatment arm, have confirmed evidence of symptomatic

improvement without survival benefit in unselected patients (Green et al. 2015). Mitoxantrone is associated with significant toxicity, including pancytopenias, fatigue, and shortness of breath (Green et al. 2015). Despite this, physicians still use it, albeit rarely, for symptom control in patients in whom treatment options may otherwise be limited. Mitoxantrone is, however, a type II topoisomerase inhibitor that impacts DNA synthesis and DNA repair and is likely to be most active in prostate cancers with DNA repair defects. Further studies evaluating whether mitoxantrone is most active against prostate cancer with defects in DNA repair mediated by HR are now warranted.

Novel Hormone Therapies

It is well established that androgen signaling plays a pivotal role in both hormone-sensitive prostate cancer and mCRPC. Several aberrations of the AR have been identified in mCRPC, including gene amplification, overexpression, rearrangements, splice variants, and activating mutations. These aberrations likely contribute to persistent AR signaling despite castrate levels of testosterone. Identification of compounds targeting this pathway has provided us with several drugs of important clinical significance, including abiraterone and enzalutamide, which now both have regulatory approval (Scher et al. 2010; de Bono et al. 2011). Furthermore, as both drugs are orally available and generally well tolerated, the ease of administration makes them a preferred option for many patients.

The formation of AR splice variants (of which AR-V7 is the most studied) appears to be a major factor contributing to castration resistance. These variants, which have been associated with resistance to abiraterone and enzalutamide (Antonarakis et al. 2014), lack the ligand-binding domain of the AR, but remain constitutionally active. It has been shown that AR-V7 expression is higher in patients with advanced prostate cancer after castration and even more after abiraterone/enzalutamide, and that higher levels associate with treatment resistance and poor prognosis (Efstathiou et al. 2015; Welti et al. 2016). However, further prospective work exploring the significance of AR splice variants, including AR-V7 with agents targeting these, are needed for further validation. Critically, analytically validated and practical assays to determine the presence of these splice variants are now urgently needed to establish this putative predictive biomarker.

Abiraterone

Abiraterone acetate is an irreversible, selective cytochrome p450 17A1 (CYP17) inhibitor that blocks steroid conversion and therefore androgen production within the prostate, testis, and adrenal gland (Attard et al. 2005). Several large phase III studies have confirmed the antitumor activity of abiraterone as an effective treatment for men suffering from CRPC (de Bono et al. 2011; Fizazi et al. 2012; Ryan et al. 2012) with improvement in OS of almost 5 months in the postchemotherapy setting. Preclinical data indicate that abiraterone acetate is metabolized to generate a potent AR antagonist that is at least as potent at blocking AR as enzalutamide, which suggests that this agent not only blocks CYP17 but also AR directly (Li et al. 2015, 2016).

Abiraterone is orally available and taken at a dose of 1000 mg/day, in combination with a low dose of oral prednisolone. In approximately one-third of patients, a "steroid switch" from prednisolone to low-dose dexamethasone at the point of progression showed reversal of resistance, with patients showing durable PSA and radiological responses following the change in steroids. The rationale behind this treatment switch is secondary to abiraterone resistance being the result of AR point mutations activated by prednisolone but not dexamethasone, as well as glucocorticoid receptor activation, which is also lower with dexamethasone (Lorente et al. 2014). Common side effects of abiraterone are linked to increased mineralocorticoid levels induced by CYP17 blockade, and include hypertension, hypokalemia, and fluid retention (Fizazi et al. 2012). Low-dose oral steroids such as prednisone/prednisolone 5 mg twice daily or dexamethasone 0.5 mg/day can abrogate these side effects. The latter may indeed be preferable be-

cause it has a longer half-life and is less likely to activate the mineralocorticoid receptor, or mineralocorticoid receptor antagonists that do not bind the AR such as eplerenone can be used. The mineralocorticoid antagonist spironolactone is an AR agonist and must be avoided in this patient population. There is also a small risk of transaminase elevation with abiraterone treatment and, consequently, liver function should be monitored in the first 12 weeks.

Enzalutamide

Enzalutamide (MDV3100) (Tran et al. 2009) is a novel antiandrogen that offers a treatment advantage over standard antiandrogens antagonizing full-length AR and preventing AR nuclear translocation, AR binding to DNA, and coactivator recruitment by AR. Large phase III trials (including AFFIRM and PREVAIL) have shown significant antitumor activity with improvement in OS in both the pre- and postchemotherapy settings (Scher et al. 2012; Beer et al. 2014).

Enzalutamide is taken orally, once daily, at a dose of 160 mg. Common side effects include fatigue, gastrointestinal disturbance, and hot flushes. More serious, rarer side effects include seizures, which have been reported in <1% of patients treated with enzalutamide (Hoffman-Censits and Kelly 2013) and may be as infrequent as impacting 0.1% of patients. Enzalutamide does appear to potently penetrate the blood–brain barrier and has been reported to significantly cause neurocognitive deficits and significant fatigue, although these are usually reversible.

Abiraterone versus Enzalutamide

Superiority of either drug has not as of yet been shown, and patient preference and comorbidities play a large role in treatment choice. Abiraterone is best avoided in patients with cardiovascular disease because of the mineralocorticoid side effects listed above. Similarly, because of the risk of seizures, treatment with enzalutamide is not advised in patients who have preexisting structural brain damage or known seizure activity. Moreover, in patients with jobs requiring substantial intellectual engagement, abiraterone may be preferable to enzalutamide. A recent randomized trial reports an increased prevalence of these side effects in patients on enzalutamide (Chi 2016). Overall, however, both of these drugs are generally well tolerated.

Some studies have shown evidence that a small number of patients do respond to abiraterone post-enzalutamide, and indeed to enzalutamide post-abiraterone, but these figures have been much lower than predicted, with response rates in the region of 10% to 15% (Loriot et al. 2013; Schrader et al. 2014). This is likely caused by cross-resistance between these agents (Fizazi et al. 2012) and the formation of AR splice variants (Mostaghel et al. 2011). Lower response rates mean that, in many health-care settings, treatment with either abiraterone or enzalutamide is not currently approved if the patient has already received the other novel endocrine agent (enzalutamide or abiraterone).

Radium-223

Radium-223, also known as alpharadin, is a radioisotope that emits high-energy alpha particles over a short range (<100 μm); these induce double-strand DNA breaks in adjacent tumor cells, while sparing normal tissue without a significant bystander effect. The phase III ALSYMPCA trial (alpharadin in symptomatic prostate cancer) showed a significant improvement in OS (of almost 3 months) compared with treatment with placebo from radium-223. Radium-223 also delayed symptomatic skeletal events and improved quality of life (Parker et al. 2013).

Radium is given as four weekly intravenous infusions for a total of six cycles (Parker et al. 2013), although the optimal dose, schedule, and duration of treatment with this agent is not yet well defined. Because of its highly localized activity, radium-223 has a favorable side-effect profile and is generally well tolerated. Common side effects seen include fatigue, gastrointestinal disturbance, and bone pain. Hematological toxicity, including anemia, thrombocytopenia, and leucopenia, can be seen due to effects on adjacent bone marrow. However, this is usually mild and can be treated with supportive treatment

until the bone marrow recovers (Wissing et al. 2013b).

Although the highly targeted therapy that alpharadin delivers is beneficial in terms of side effects, it is important to remember that eligibility for ALSYMPCA included only symptomatic mCRPC patients with bony metastases and no visceral disease (Sartor et al. 2014). Therefore, radium-223 is not a recommended treatment for patients who have disease outside of their skeleton, that is, nodal (>3 cm in short-axis) or visceral metastases or large volume soft tissue disease. Developments in alpha-particle-emitting radioimmunoconjugates are likely to further transform the treatment of advanced prostate cancer, for example, with antibodies to prostate-specific membrane antigen (PSMA) linked to alpha particles emitting radioisotopes showing a huge potential for patient benefit. The usage of gallium-PSMA positron-emitting-tomography (PET) may be a useful predictive biomarker for these agents (Kratochwil et al. 2016).

Sipuleucel-T

Sipuleucel-T is currently the only form of immunotherapy approved for the treatment of mCRPC, and the first therapeutic cancer vaccine to be approved by the FDA. This is an autologous dendritic cell vaccine whereby a patient's peripheral blood mononuclear cells, including antigen-presenting cells, are initially extracted by leukapheresis. These are then activated ex vivo with a fusion protein (PA202), which contains prostate acid phosphatase and granulocyte macrophage colony-stimulating factor. The activated product is then infused back into the patient, and this infusion triggers the patient's own immune response into attacking their disease (Di Lorenzo et al. 2012). Several positive studies have indicated that this agent has antitumor efficacy, including a small phase III trial that showed an improvement in OS of more than 4 months in patients randomized to sipuleucel-T versus placebo (Kantoff et al. 2010), although some concerns have been raised about the design of this trial (Huber et al. 2012). Questions regarding its efficacy and side-effect profile, as well as high cost because of the expensive cost-of-production (estimated at ~$35,000 per cycle [Simpson et al. 2015]), have meant that this drug has not been widely used.

Based on evidence from clinical trials, the FDA-recommended dosage should be for three complete doses to be given via infusion at approximately 2-week intervals. Side effects include those associated with the initial leukapheresis procedure to harvest the patient's mononuclear cells (e.g., bleeding, bruising, and light-headedness), the infusion (e.g., rigors and pyrexia), and treatment itself (commonly fatigue, nausea, and headache) (Kantoff et al. 2010; Small et al. 2013).

SYMPTOMATIC THERAPY

Although the therapies discussed above all offer a degree of survival benefit, it is vital to remember that symptom control is of paramount importance. Patients should have input from their community palliative care team as early as possible, and ideally this must be part of the overall multidisciplinary care team (Bader et al. 2012; Scotté 2012). Other medical interventions, such as blood transfusions for symptomatic anemia and radiotherapy for painful bony metastases, must also be regularly considered. Finally, in patients with metastatic disease at diagnosis who never get their prostate primary treated early in the treatment process, due consideration needs to be given to local control as early as possible to abrogate potentially devastating local complications such as urinary obstruction and fistulae formation (Donovan et al. 2016). Randomized phase III trials such as STAMPEDE have evaluated whether local therapy in patients with M1 disease at diagnosis impacts outcome and quality of life; the results of these studies are eagerly awaited but in the interim the treatment of the primary disease must not be forgotten in this subgroup of patients with aggressive disease.

FUTURE THERAPIES

Unfortunately, the prognosis of mCRPC patients and their OS rates, despite these recent advances in treatment, remain bleak. Although there are a plethora of treatments now available

for mCRPC, realistically these agents all provide only relatively small survival benefits. It has been recognized that the landscape of prostate cancer is evolving; increased understanding of the heterogeneity of the disease and the identification and validation of predictive biomarkers would allow optimization of treatment with patient-specific targeted therapies (Lorente et al. 2015; Robinson et al. 2015).

The development of next-generation sequencing techniques have driven significant advances in our understanding of the genomics of cancer and allowed for novel therapies to be developed. Robinson et al. (2015) showed the mutational landscape of mCRPC by performing whole-exome and transcriptome sequencing of biopsy specimens from 150 mCRPC patients. Many oncogenic mutations were identified in the vast majority of patients, including those affecting the AR pathway (63%), PI3K pathway (49%), and DNA repair pathway (23%), to name but a few. Actionable aberrations were identified in the vast majority of patients, and the importance of performing fresh biopsies in patients was shown, as many of these mutations had not been present in their primary prostate cancers (Gundem et al. 2015). Identification of actionable biomarkers in the metastatic setting could allow for precision medicine, that is, patient-specific targeted therapy to be administered with the goal of improving prognosis. Distinguishing between actionable aberrations allows us to better explore further treatment options.

PTEN/AKT Pathway

It is widely accepted that many patients with mCRPC (~50%) have activation of the PI3K/AKT pathway, which plays a vital role in tumor growth, proliferation, and survival, and also in resistance to therapy (Bellacosa et al. 2005; Manning and Cantley 2007). Functional loss of PTEN, a protein that down-regulates this pathway, is thought to be present in >40% of metastatic prostate cancers, because of gene deletions, methylation, micro-RNA (miRNA) expression, mutations, and posttranslational modifications (Yoshimoto et al. 2012). It has also been shown that PTEN loss is associated with advanced disease and poor outcome (Ayala et al. 2004; Reid et al. 2010; Yoshimoto et al. 2012; Ferraldeschi et al. 2015). Furthermore, studies have shown cross talk between the PI3K pathway and AR signaling, showing that PTEN loss results in increased AKT activation and up-regulation of AR signaling through p110β (Carver et al. 2011; Schwartz et al. 2015). These studies, and others, have provided a strong rationale for developing combination strategies targeting this pathway. Preclinical and phase I studies have been conducted to test single-agent AKT inhibitors, with modest results thus far (Chen et al. 2006; Dienstmann et al. 2011). The reasons for this are likely multifactorial, and include cross talk between signaling pathways and tumor heterogeneity. This highlights the need for further trials exploring combination therapies, which are currently ongoing, combining p110β and AKT inhibitors with next-generation AR antagonists, including abiraterone and enzalutamide.

DNA Repair Pathway

Mutations in DNA repair have also been identified in mCRPC, and have important clinical implications. It is now well established that genes involved in HR, including *BRCA2*, *BRCA1*, *PALB2*, and *ATM* are commonly deleteriously aberrant in this disease. It has also been reported that patients with deleterious germline *BRCA2* mutations are at increased risk of prostate cancer (Struewing et al. 1997; Gallagher et al. 2010). Additionally, germline *BRCA1* and *BRCA2* mutations are associated with both higher grade and stage of cancer at diagnosis, and worse outcomes (Gallagher et al. 2010; Castro et al. 2015). MMR defects have also been reported in this disease, with Lynch syndrome carriers of deleterious aberrations of MMR genes also associating with increased prostate cancer risk (Pritchard et al. 2014; Ryan et al. 2014). These DNA repair defects open a therapeutic avenue with immunotherapy strategies (Graff et al. 2016).

PARP Inhibition

Targeting cancers with defects in HR repair has also opened doors for the treatment of mCRPC.

A trial reported in 2015 showed the antitumor activity of olaparib, a poly(adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitor, in patients with both somatic and germline aberrations in *BRCA* and other genes involved in HR DNA repair (Mateo et al. 2015). PARP is an enzyme that is key to DNA repair, and PARP enzyme inhibition has already been established as a treatment for ovarian cancers, with studies showing durable objective responses and improvement in progression-free survival in sporadic high-grade serous ovarian cancers (Gelmon et al. 2010; Ledermann et al. 2012). This study by Mateo and colleagues in mCRPC patients enrolled 50 patients with late-stage disease (all of whom had received prior docetaxel and either abiraterone or enzalutamide, as well as a further 58% having also received cabazitaxel), who were treated with olaparib monotherapy. Of the 49 evaluable patients, 16 responded to olaparib, with 12 receiving the drug for more than 6 months. Overall, 88% (14/16) of the responders were found to have defects in DNA-repair genes (including both biallelic somatic loss and germline mutations of *BRCA2*, as well as ATM mutations) (Mateo et al. 2015). The study has led to the FDA granting "breakthrough" designation in January 2016 to support the accelerated approval of olaparib for monotherapy of *BRCA1*, *BRCA2*, or *ATM*-gene-mutated mCRPC patients.

Olaparib is given orally in tablet form, and is generally well tolerated. Known side effects include hematological toxicity, with anemia being both the most common adverse event reported and the main reason for dose reductions in the TOPARP trial, in which 400 mg of this PARP inhibitor was administered twice daily to patients. Other toxicities, including fatigue, nausea, vomiting, and decreased appetite, have also been reported (Fong et al. 2009).

Platinum-Based Chemotherapy

Although not currently approved for treatment of mCRPC, phase II trials that include platinum-based chemotherapy in unselected mCRPC patients have shown antitumor activity (Sella et al. 2009; Hager et al. 2016). Platinum salts have, in some ways, similar mechanisms of action to PARP inhibitors, causing double-stranded DNA damage by inducing inter- and intrastrand DNA cross-links. This DNA damage and resultant tumor cell death have been shown to induce PSA and radiological response in patients, as well as increased progression-free survival to some degree in unselected patients. However, failure to optimally identify a target group may, at least in part, explain failed registration trials. A phase III trial with satraplatin, an orally bioavailable platinum compound, showed evidence of second-line antitumor activity in unselected patients, with a 50% PSA decline rate of 33% and significant progression-free survival rates in 40% of the patients (Sternberg et al. 2009). It is likely that if this trial was repeated in prostate cancer patients with DNA repair defects, then this trial would result in a survival benefit.

In ovarian cancer, the prevalence of aberrations in genes involved in HR confer sensitivity to both platinum and PARP inhibition, and patients who progress following PARP inhibition may still respond to platinum. Furthermore, it has been reported that ovarian cancer patients with nucleotide excision repair (NER) pathway defects respond to platinum while displaying PARP inhibitor resistance (Ceccaldi et al. 2015). NER defects may also be found in mCRPC, and further phase II and III studies testing the safety and efficacy of platinum-based chemotherapy in selected groups of biomarker-positive patients with differing DNA repair pathway aberrations are warranted.

Platinum chemotherapy, such as 3-weekly carboplatin given intravenously (e.g., at AUC6 or AUC5 dosage) needs further evaluation in mCRPC patients with defects in HR and in other DNA-repair pathways; preliminary data indicate that this has antitumor activity (Cheng et al. 2016). Platinum-associated side effects include hematological toxicity and nephrotoxicity, alopecia, mucositis, nausea, and vomiting (Fotopoulou et al. 2014).

Mismatch Repair Defects

In addition to defects in HR repair, other forms of DNA repair, including MMR, have been im-

plicated in mCRPC, with the prevalence of MMR aberrations estimated to be in the region of 3%–12%, depending on assay selection (Pritchard et al. 2014; Robinson et al. 2015). MMR protein loss of function (e.g., caused by mutations in *MLH1*, *MLH2*, *MSH6*) is associated with microsatellite instability and high mutational load. High-mutation frequency is thought to result in a higher burden of neoepitopes or neoantigens, which are tumor specific and allow for enhanced immune recognition. Targeting immune checkpoints, for example, inhibiting CTLA4 and PD-1, may therefore up-regulate the body's immune response (Snyder et al. 2014). A positive association has been found between tumors high in PD-L1 and total mutation load in several tumor types (Ock et al. 2016). Using immunotherapy to block the PD-1 axis is already established for the treatment of various tumor types, with nivolumab (anti-PD1) and pembrolizumab (anti-PD1) having been approved by the FDA for the treatment of melanoma and non-small-cell lung cancer (NSCLC) (Herbst et al. 2014; Tumeh et al. 2014; Robert et al. 2015; Van Allen et al. 2015). Frequent somatic mutations are a result of ultraviolet light exposure in melanoma and cigarette smoking in NSCLC. Studies have shown that in these tumor types, increased likelihood of response associates with mutational load, which can associate with the presence of deleterious DNA repair defects (Rizvi et al. 2015). Moreover, MMR loss was associated with treatment benefit from pembrolizumab in colorectal carcinomas (Le et al. 2015).

The prevalence of MMR-defective advanced prostate cancer may be higher than that described in some reports, as many studies characterizing them thus far have used whole-exome or targeted sequencing, although MMR defects in mCRPC have been shown to be commonly associated with intronic rearrangements (Pritchard et al. 2014). As higher mutational load is also associated with other DNA repair defects (Le et al. 2015), there is now a strong rationale for evaluating immunotherapy and combination strategies for targeting this subset of mCRPC.

CONCLUSIONS

This review has highlighted the challenges of treatment in the evolving landscape of mCRPC. Despite the development of several well-tolerated and efficacious treatments, these diseases remain invariably fatal, although patients are living longer than ever before. The patient and physician should make treatment decisions together, with the latter working in the context of multidisciplinary teams using all currently available evidence. Where possible, next-generation sequencing–based tumor analyses should be pursued because these are highly likely to identify specific genomic aberrations that can guide patient care. We envision that over the next decade, the treatment of advanced prostate cancer diseases will change substantially, allowing the delivery of better and more precise care for this disease.

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