STATE-OF-THE-ART TREATMENT IN CASTRATION-RESISTANT PROSTATE CANCER

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ABSTRACT

Prostate cancer (PrCa) is the most common cancer type in men in developed countries. In the last few years, a dramatic change has occurred in the understanding of castration-resistant PrCa which has led to the development of new drugs that have an impact on patient survival. This review summarises the recent advances in the management of the disease.

Keywords: Prostate cancer, renal cancer, bladder cancer, testicular cancer, treatment options.

PROSTATE CANCER (PRCA)

PrCa is the second most common cancer and the sixth leading cause of cancer mortality in men worldwide.[1] In most developed countries, PrCa has become the leading cancer in men, mainly due to lifestyle factors and the spread of prostate specific antigen (PSA) screening. During the last 25 years, the advances in PrCa diagnosis and treatment have improved 5-year survival rates from 68.3% to almost 95% when all stages are considered. Nonetheless, up to 90% of PrCa diagnosed in the developed countries are organ-confined, and the 5-year survival rates approach 100% following conventional treatments.[2] Management of localised disease includes active surveillance, radical prostatectomy, and radiation therapy (external beam radiotherapy and brachytherapy). At this time, cryosurgery or other local therapies are not recommended as primary treatments outside of a clinical trial due to the lack of long-term data comparing these treatments with radiotherapy or prostatectomy.[3] The availability of several therapeutic options for localised stages warrants careful consideration when planning treatment with curative intent. Patients need to be active participants in decision-making, and they must be aware of the benefits and possible complications of the different types of treatment. With better survivorship, the focus is now towards the reduction of treatment-related morbidities and better individualisation of treatment options according to disease biology.[2]

Androgen deprivation therapy (ADT) is the cornerstone of treatment for patients with advanced PrCa. Unfortunately, in the majority of cases this will only provide temporisation and palliation. The natural evolution of PrCa is due to castration-resistant prostate cancer (CRPC), a lethal form of the disease. Significant gains in our understanding of the pathogenesis of CRPC have occurred in the last decade, which has led to the development of new agents that impact on overall survival (OS). Docetaxel + prednisone, every 3 weeks, is the preferred first-line chemotherapy treatment for symptomatic CRPC.[3] No consensus exists for the best subsequent therapy for metastatic CRPC (mCRPC) after docetaxel failure. Options include abiraterone, enzalutamide, cabazitaxel, radium-223, docetaxel rechallenge, mitoxantrone, sipuleucel-T, and participation in clinical trials.

Cytotoxic Chemotherapy

Docetaxel

Docetaxel was the first chemotherapy approved for mCRPC that showed a survival benefit. In 2004, two studies compared docetaxel with mitroxantrone, the previous standard of care. In the SWOG 99-164 and TAX3275 studies, docetaxel extended OS by 2 months and showed a significant improvement in time to progression and PSA decline. The TAX327 study compared docetaxel given every 3 weeks and weekly docetaxel with mitoxantrone given every 3 weeks (all drugs were administered with prednisone). Only 3-week docetaxel demonstrated survival benefit over mitroxantrone, whilst PSA response rate and quality of life (QoL) scores were significantly improved in both docetaxel groups. Since these studies, multiple trials have been conducted with different agents in combination with docetaxel for mCRPC (e.g. bevacizumab, aflibercept, lenalidomide, dasatinib, and sunitinib) but none have shown improvement in OS compared with docetaxel and prednisone.[6]

Docetaxel has not been commonly used for asymptomatic patients, except for those with signs of rapid progression or liver involvement,[3] and with the advent of new treatments such as abiraterone and enzalutamide, which have proven to benefit chemo-naïve mCRPC patients, the administration of docetaxel tends to be delayed. Interestingly, a new study has recently addressed the question of whether upfront chemotherapy also confers an OS advantage for PrCa patients. The CHAARTED trial randomised 790 patients with hormone-sensitive metastatic PrCa to ADT alone versus ADT + docetaxel 75 mg/m^2 every 3 weeks for six cycles. The primary endpoint was OS. It was found that ADT + docetaxel resulted in a median OS of 57.6 months versus 44 months in the ADT alone arm (HR 0.61, p=0.0003). Although ADT + docetaxel was beneficial in all subgroups analysed, the benefit was more important for patients with high-volume disease. In this subgroup of patients median OS was 49 months with docetaxel + ADT versus 32 with ADT alone (HR 0.60, p=0.0006). Median time to clinical progression was 33 months when docetaxel was added versus 20 for ADT alone (HR 0.49, p<0.0001). Similarly, median time to CRPC was 21 months in the ADT + docetaxel arm versus 15 in the ADT-only arm.[7]

There is a need for better identification of which patients should be considered with 'high' and 'low' metastatic volume disease. To date, the 17-month difference in OS, observed in the high-volume disease group, is the greatest improvement in survival reported for PrCa.

Cabazitaxel

The Phase III trial (TROPIC)[8] that led to the approval of cabazitaxel by the regulatory agencies in 2010, randomised 775 mCRPC patients to cabazitaxel 25 mg/m^2 or mitroxantrone 12 mg/m^2 each with daily prednisone.[9] Patients had previously received docetaxel. At 2.4 months, improvement in OS was demonstrated with cabazitaxel compared to mitoxantrone (HR 0.72; p<0.001). Febrile neutropaenia was observed in 7.5% of cabazitaxel-treated men versus 1.3% in the mitroxantrone arm, indicating the need for vigilance and treatment, or prophylaxis to prevent febrile neutropaenia.[8] The incidences of severe diarrhoea (6%), fatigue (5%), nausea/vomiting (2%), anaemia (11%), and thrombocytopaenia (4%) were also higher in cabazitaxel-treated men.[9]

Second-Generation Anti-Androgens

Abiraterone

Abiraterone acetate is an irreversible inhibitor of CYP17 that blocks androgen synthesis in the testis, adrenal glands, and prostate, but also leads to undetectable intratumoural androgen levels.[10] Abiraterone has an antitumour effect on both chemotherapy-treated and chemotherapy-naïve CRPC patients. The COU-AA-301 study[11] randomised mCRPC patients who had progressed post-docetaxel to abiraterone + prednisone or placebo + prednisone. The use of prednisone with abiraterone is necessary due to the mineralocorticoid-related adverse events (AEs). Abiraterone demonstrated prolonged OS (14.8 versus 10.9 months, HR 0.65, p<0.001), time to PSA progression (10.2 versus 6.6 months), progression free survival (5.6 months versus 3.6 months), and a greater PSA response rate (29% versus 6%).

Abiraterone has also been investigated in the chemo-naïve setting. In the COU-AA-302 study, CRPC patients with PSA or radiographic progression were randomised to abiraterone + prednisone or placebo + prednisone.[12] Most patients in this trial were not taking opiates for cancer pain and none had visceral metastatic disease or ketoconazole exposure. Primary endpoints were

radiographic progression free survival (rPFS) and OS. The study was unblinded at the time of a planned interim analysis after 43% of the expected deaths had occurred. The rPFS was significantly improved in the abiraterone group (16.5 versus 8.3 months, HR 0.53, p<0.001). There was a 25% decrease in the risk of death in the abiraterone group, which showed a trend toward OS improvement from 27.2 months for placebo to not reached (HR 0.75, p=0.01). However, this did not meet pre-specified statistical significance. Abiraterone prolonged median time to initiation of cytotoxic chemotherapy, median time to opiate use for cancer-related pain, PSA progression, and decline in performance status.

The most common adverse reactions seen with abiraterone were fatigue (39%), back or joint discomfort (28-32%), peripheral oedema (28%), diarrhoea, nausea or constipation (22%), hot flushes (22%), hypertension (22%, severe hypertension 4%), hypokalaemia (17%), and atrial fibrillation (4%). Increased aspartate aminotransferase, and/or alanine aminotransferase, or cardiac disorders (heart failure, arrhythmias, and myocardial infarction in 19%, serious in 6%) were the most common adverse drug reactions that resulted in drug discontinuation; therefore, potassium levels and blood pressure readings on a monthly basis are warranted during abiraterone acetate therapy. Symptom-directed assessment for cardiac disease is also warranted, particularly in patients with pre-existing cardiovascular disease.[3] Although the use of abiraterone in the pre-docetaxel setting in patients with asymptomatic or minimally symptomatic CRPC is supported by these results, its use in men with symptomatic or visceral disease has not been formally assessed in a controlled trial or compared with docetaxel chemotherapy yet.[3]

Enzalutamide

Enzalutamide is a pure androgen receptor (AR) antagonist and, unlike first-generation anti-androgens such as bicalutamide and flutamide, it has a greater affinity for the receptor and no known agonistic effect.[13]

The AFFIRM study compared enzalutamide to placebo in mCRPC patients previously treated with docetaxel and who had biochemical or radiographic progression.[14] This trial randomised 1,199 patients to enzalutamide or placebo in a 2:1 ratio and the primary endpoint was OS. The study was stopped after a planned interim analysis at the time of 520 deaths. Median OS was 18.4 months in the enzalutamide arm compared to 13.6 in the placebo group (HR 0.63, p<0.001), with a 37% reduction in risk of death. Survival was improved in all subgroups analysed, including men with poor performance status, high or low PSA levels, visceral metastasis, significant pain, and more than two prior chemotherapy regimens. Enzalutamide was also superior to placebo in the proportion of patients with >50% PSA decline (54% versus 2%), time to PSA progression (8.3 versus 3.0 months), radiographic response (29% versus 4%), rPFS (8.3 versus 2.9 months, HR 0.40, p<0.001), and the time to the first skeletal-related event (16.7 versus 13.3 months, HR 0.69, p<0.001). QoL was also improved with enzalutamide compared to placebo. AEs were mild and included fatigue (34% versus 29%), diarrhoea (21% versus 18%), hot flashes (20% versus 10%), and headache (12 versus 6%). Five patients on enzalutamide had seizures compared to none in the placebo group (0.6 versus 0%). The incidence of cardiac disorders did not differ between the two arms.

In the pre-docetaxel setting, the PREVAIL study[15] randomised 1,717 patients with asymptomatic or mildly symptomatic metastatic chemo-naïve CRPC to enzalutamide or placebo. Approximately 12% of patients had liver and/or lung metastasis. Primary aims were OS and rPFS. The interim analysis at 539 deaths showed a statistically significant benefit of enzalutamide over placebo with a 29% reduction in risk of death and an 81% reduction in risk of radiographic progression. In addition, enzalutamide showed success in completely or partially reducing soft tissue disease on imaging in 59% of patients (20% complete responses and 39% partial responses). Enzalutamide also delayed the median time to chemotherapy initiation by 17 months.

Grade 3-4 AE rates were similar in both arms; AEs that occurred slightly more often with enzalutamide included all-grade fatigue (36% versus 26%), back pain (27% versus 22%), constipation (22% versus 17%), and arthralgia (20% versus 16%). Although patients with a history of seizure were excluded from the study, one seizure occurred in each arm of the trial, both in patients with a history of seizure that was unknown at time of enrolment.[15] To assess the real incidence of seizures and monitor the safety of enzalutamide, the 9785-CL-0403 Phase IV study is currently enrolling CRPC patients known to have risk factors for seizure.[16]

Both abiraterone and enzalutamide have independently demonstrated clinical benefit, and thus, represent a standard of care for CRPC after docetaxel failure, provided these agents were not used pre-docetaxel. Aside from practical considerations (i.e. contraindications to steroids, and potential side-effects), there are currently no head-to-head data informing which agent may excel in a given patient. However, despite their efficacy, not all patients respond to these treatments, and neither abiraterone nor enzalutamide are curative, and resistant disease eventually develops.

The AR isoform encoded by splice variant 7 (AR-V7) lacks the ligand-binding domain, which is the target of both enzalutamide and abiraterone, and remains constitutively active as a transcription factor. The detection of AR-V7 in circulating tumour cells from patients with CRPC has been associated with resistance to both abiraterone and enzalutamide.[17] Several studies have also shown that mutant AR can become promiscuously activated by very low levels of androgens, other steroid metabolites, and drugs that bind the AR. These models support co-targeting combinations of CYP17 inhibitors with other enzymatic inhibitors or with potent second-generation AR antagonists. Combined therapy of abiraterone + enzalutamide is currently an area of great interest, although there are some data suggesting cross-resistance between abiraterone and enzalutamide.[18,19] On the other hand, given the evidence of a reciprocal feedback loop between the AR and the PI3K/Akt pathway,[20] combination of novel AR-targeted drugs enzalutamide and abiraterone acetate with PI3K/Akt inhibitors appears to hold great promise.[21] Further understanding of the mechanisms that underlie acquired and primary resistance is a priority to inform on the development of the next therapeutic strategies.

Inmunotherapy

Sipuleucel–T became the first in a new class of cancer immunotherapeutic agents to be approved by the FDA. It is an autologous cancer 'vaccine' that involves a collection of the white blood cell fraction containing antigen-presenting cells from each patient; exposure of the cells to the prostatic acid phosphatase-granulocyte macrophage colony-stimulating factor (PAP_GM_CSF recombinant fusion protein); and subsequent reinfusion of the cells. The pivotal study (D9902B) randomised patients with minimally symptomatic or asymptomatic mCRPC to receive sipuleucel-T or placebo. Sipuleucel-T treatment resulted in a 22% reduction in mortality risk, with 25.8 months median OS in the vaccine arm versus 21.7 in the control arm. AEs included mild-to-moderate chills, pyrexia, and headache. Additional data showed that this benefit was present in almost every subset of patients; across Gleason score, PSA, extent of disease, age, and laboratory values. Sipuleucel-T is recommended for mCRPC patients without symptoms, with good performance status (ECOG 0-1), and at least 6 months of estimated life expectancy. Treatment subsequent to sipuleucel-T should proceed as clinically indicated, particularly in the occurrence of symptoms.

Ipilimumab is a fully human monoclonal antibody that inhibits CTLA-4. In mCRPC post-docetaxel patients, a Phase III study randomising patients to receive bone-directed RT, before either ipilimumab or placebo, failed to show OS benefit.[22] Subset analyses showed that ipilimumab may be most active in men with lower disease burden, similarly to sipuleucel-T.

Agents Related to Bone Health in CRPC

Bone metastases are a major cause of morbidity and mortality in men with PrCa including pathologic fracture, spinal cord compression, and debilitating bone pain requiring additional therapy. Besides, ADT results in accelerated bone resorption, leading to bone loss and an increased risk of fracture. Excessive osteoclast activity plays a central role in the pathophysiology of bone disease at each stage of PrCa disease progression. Zoledronic acid, a highly potent inhibitor of osteoclast-mediated bone resorption, increases bone mineral density in men receiving ADT. In a multicentre study, 643 men with CRPC and asymptomatic or minimally symptomatic bone metastases were randomised to 4 mg zoledronic acid every 3 weeks or placebo.[23] At 15 months, 33% of patients on zoledronic acid presented with skeletal related events (SRE) compared with 44% of patients in the placebo arm (p=0.02). Zoledronic acid also delayed the occurrence of first SRE. No significant differences were found in OS.[24] Zoledronic acid is restricted in patients with renal impairment as it has the potential to cause renal insufficiency. Other bisphosphonates (pamidronic and clodronic acid) have not shown to be effective in preventing disease-related skeletal complications.[3]

Denosumab, a fully human monoclonal antibody with high affinity and specificity for human RANKL, inhibits bone resorption, including in those who failed prior bisphosphonate treatment. Denosumab has been compared to zoledronic acid in men with CRPC.[25] The absolute incidence of SREs was similar in the two groups; however, the first SRE was delayed by 3.6 months by denosumab compared to zoledronic acid. Although the rates of important SREs and treatment-related toxicities were similar with both compounds, including osteonecrosis of the jaw (1% versus 2%, p=0.09) and arthralgias, hypocalcaemia was more common with denosumab (13% versus 6%, p<0.0001). Zoledronic acid, or denosumab, is recommended for men with CRPC and bone metastases to prevent or delay disease-associated SRE, although the optimal duration of the therapy remains unclear.[3] Clinical research continues on the prevention or delay of disease spread to bone. In a Phase III randomised trial involving patients with non-mCRPC, denosumab increased bone-metastasis-free survival by a median of 4.2 months compared with placebo and delayed time to first bone metastasis, but failed to improve OS, and the regulatory agencies have not approved this indication for denosumab.[26]

Recently, a first-in-class radiopharmaceutical compound has been approved for treatment of mCRPC in patients with symptomatic bone metastasis and unknown visceral metastatic disease. In these patients, radium-223 has shown to improve OS by almost 4 months, and to prolong time to first symptomatic SRE.[27] Radium-223 dichloride is a targeted alpha emitter that selectively binds to areas of increased bone turnover in bone metastases and emits high-energy alpha particles of short range (<100 µm). As a bone-seeking calcium mimetic, radium-223 is bound into newly formed bone stroma, especially within the microenvironment of osteoblastic or sclerotic metastases. The high-energy alpha-particle radiation induces mainly double-stranded DNA breaks that result in a potent and highly localised cytotoxic effect in the target areas. The short path of the alpha particles also means that toxic effects on adjacent healthy tissue, and particularly the bone marrow, may be minimised.

In the pivotal Phase III study (ASYMPCA) that led to the drug's approval, patients that had previously received docetaxel - or were ineligible for it - were randomised 2:1 to six monthly radium-223 intravenous or placebo every 4 weeks. The primary endpoint was OS. The main secondary efficacy endpoints included time to the first symptomatic SRE and various biochemical endpoints. Radium-223 significantly improved OS as compared with placebo (14.9 versus 11.3 months, HR 0.70, p<0.001) and prolonged time to first symptomatic SRE (15.6 versus 9.8 months). Grade 3-4 haematologic toxicity was low (3% neutropaenia, 6% thrombocytopaenia, 13% anaemia). Radium-223 can be used with denosumab or a bisphosphonate, but its combination with chemotherapy outside of a clinical trial has the potential for additive myelosuppression.[3]

CONCLUSION

The significant gains in our understanding of the pathogenesis of PrCa have led to the development of new agents that have an impact on OS of CRPC patients. These treatments that are currently available in daily clinical practice have totally changed the management of the disease in barely 5 years. There remain many questions, particularly regarding the optimum timing and the most appropriate sequencing and/or combinations of second-generation anti-androgens and immunotherapeutics with conventional anti-androgen therapy and cytotoxic chemotherapy therapy. The overall therapeutic goal is to maximise treatment effect while minimising toxicity. Further research to select those patients most likely to benefit from each therapy are urgently needed.

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