CHEMOTHERAPY AND NEW DRUGS IN PROSTATE CANCER

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INTRODUCTION

Prostate cancer (PrC) is the fourth most common cancer (for both sexes combined) and the second most common cancer in men (accounting for 15% of all new male cancer cases), with a worldwide incidence of approximately 1,111,200, a 5-year prevalence of 3,924,000, and a mortality incidence of 307,000 for the year 2012.1 Since the 1990s, the increasing use of prostate-specific antigen (PSA) testing has had a significant influence on incidence rates, much more so than on mortality rates.1 As diagnosis can be established very early in the disease, most cases of PrC are treated at a localised stage with very good 10-year relative survival and progression-free survival (PFS) rates.

However, some men might develop advanced or metastatic disease at diagnosis or following initial treatment, requiring the use of systemic therapy including chemotherapy in some cases. According to the Surveillance, Epidemiology, and End Results Program (SEER) database for the period 2004-2010, 81% of PrC patients in the USA were diagnosed with local disease, and only 12% and 4% presented with regional and metastatic disease at diagnosis, respectively.2 Advances in clinical research have led to the development of several strategies to manage advanced PrC. This review aims to summarise the current standard of care (SoC) for chemotherapy use in castration-resistant prostate cancer (CRPC) or hormone-sensitive prostate cancer, in light of the available new hormonal treatments.

As opposed to many other malignancies, cytotoxic chemotherapy (CC) in PrC has no place as a neoadjuvant treatment modality in 2015. However, within the last two decades, taxane-based combination regimens have emerged as significant therapeutic options in metastatic CRPC (mCRPC). Chemotherapy in PrC primarily includes docetaxel and cabazitaxel, both taxanes. In 2015, during the last European Association of Urology (EAU) meeting in Madrid, the EAU published the latest version of their guidelines for the management of PrC, based on a systematic review of all the available clinical evidence to date.3 The current guidelines mainly reserve the use of docetaxel chemotherapy for patients with mCRPC, as first-line and second-line treatment modalities. The American Urology Association (AUA) also only recommended docetaxel-based chemotherapy but mainly in symptomatic mCRPC.4,5 Mitoxantrone was recommended by the AUA in mCRPC patients with good performance status and who were not eligible for docetaxel therapy, but mitoxantrone only confers a quality of life (QoL) benefit and no survival benefit.

HIGH-RISK/LOCALLY ADVANCED PROSTATE CANCER

While androgen deprivation therapy (ADT) combined with radiotherapy provides significant and sustained positive clinical outcomes in men with advanced disease, most patients will develop resistances to hormone therapy over time, as is the case with most hormone-dependant malignancies.
To date, only two studies have evaluated the use of chemotherapy as an adjuvant modality to radiation therapy, but current evidence shows that this therapeutic strategy only generated inconclusive findings in terms of clinical outcomes and additional toxicity. In the GETUG12 trial, which included 413 patients with high-risk local disease, radiation therapy was combined with either ADT plus a combination regimen of docetaxel, estramustine, and prednisone, or ADT alone. No significant difference in the overall survival (OS) rate (median follow-up of 7.6 years) was observed.

Another clinical study (the RTOG 99-02 clinical trial) evaluated the added benefit of the combination of paclitaxel, etoposide, and estramustine to long-term ADT plus radiation therapy, versus ADT plus radiation therapy alone in 397 patients with high-risk localised PrC. The study was terminated early due to toxicity in the form of accrued thromboembolic toxicity, as well as haematological and gastrointestinal toxicity. In non-metastatic CRPC, chemotherapy has no place and should only be considered in experimental clinical trials in locally advanced situations, as advised by AUA and EAU guidelines.

Chemotherapy in Metastatic Prostate Cancer

Metastatic Castration-Sensitive Prostate Cancer

In a small proportion of patients, most presenting with high-grade disease, PrC can progress to metastatic PrC (mPrC). While localised and regional PrC are associated with a nearly 100% rate of 5-year relative survival, OS drops to 72% at 2 years and 28% at 5 years in mPrC. In newly diagnosed mPrC, the first-line treatment modality is ADT, as the disease is generally castration-sensitive. However, in high-volume metastases, additional OS benefit could be obtained with a taxane, docetaxel, combined with prednisone and used as an adjuvant therapy, as suggested by the CHAARTED trial.

In the CHAARTED trial, conducted by the Eastern Cooperative Oncology Group (ECOG), 790 men with treatment-naïve, castration-sensitive mPrC, of which 65% had high-volume metastases (mPrC with visceral metastases or more than four bone metastases and at least one bone metastasis beyond the pelvis and vertebral column), were assigned to either combination therapy with ADT and docetaxel (six cycles of docetaxel 75 mg/m² every 3 weeks) or to ADT alone. After a median follow-up of 29 months, early results indicate that the combination arm demonstrated a significant OS advantage over ADT alone (median: 57.6 versus 44.0 months; hazard ratio [HR]: 0.61; 95% confidence interval [CI]: 0.47-0.80). Between high-volume and low-volume patients, the HRs were comparable (0.60 versus 0.63, respectively) but no statistical significance was reached in low-volume disease patients. However, a full publication is awaited in order to fully interpret the results.

The GETUG15 trial is a randomised, open-label Phase III study attempting to address the same question as the CHAARTED trial. A total of 375 castration-sensitive mPrC patients were randomly assigned to receive ADT or ADT plus docetaxel (nine cycles of docetaxel 75 mg/m² every 3 weeks). The difference in median survival between both arms was not statistically significant (46.5 versus 60.9 months, respectively; HR: 0.9; 95% CI: 0.7-1.2) after a median follow-up of 82.9 months. The updated data from GETUG15 now uses the same definition of disease extent as in CHAARTED. After a median follow-up of 82.9 months, there was no statistical difference in median OS for the high-volume disease group (35.1 versus 39.0 months; HR: 0.8; 95% CI: 0.6-1.2). This difference between the two trials might partly be explained by the differences in subsequent treatment. It is still unclear whether docetaxel should be systematically used with ADT in a subgroup of castration-sensitive mPrC patients. This should at least be discussed in the high-volume situations. Further clinical data such as the expected STAMPEDE trial, the full paper from CHAARTED, and possibly a formal meta-analysis will be needed to fully interpret the results and the role of chemo-hormonal therapy in this clinical setting.

Metastatic Castration-Resistant Prostate Cancer

In the last decade, multiple therapeutic options were developed to address mCRPC, in the form of agents targeting the androgen pathway (abiraterone and enzalutamide), radium-223, vaccine (sipuleucel-T), and taxane-based chemotherapy (Table 1). All of the above-cited approaches except sipuleucel-T have demonstrated improved outcomes in terms of radiographic PFS. All including sipuleucel-T demonstrated a significantly prolonged OS, highlighting the weak link between PFS and survival. However, there
is no evidence of superiority of one therapeutic modality over the others as no formal head-to-head comparison is available. Furthermore, the inclusion criteria are different across the trials. In all cases, the EAU and AUA guidelines endorse multidisciplinary team management.4,5,8

The choice of therapy for mCRPC is not clearly defined and depends on the metastatic disease presentation, namely metastasis extent (especially the visceral locations), symptoms, localisation and rate of progression, possibly also the speed of progression, as well as the toxicity profile of each approach relative to the side-effects-associated burden already experienced by the patient, associated comorbidities, performance status, and patient preference. Abiraterone and enzalutamide were both evaluated in chemotherapy-naïve patients19,20 and patients failing chemotherapy with docetaxel14,36 and demonstrated activity in both clinical settings. Radium-223 therapy is reserved for patients with extensive symptomatic bone metastases but no known visceral metastases.4,5,21,22

**Docetaxel in chemotherapy-naïve metastatic castration-resistant prostate cancer**

In chemotherapy-naïve mCRPC, the SoC was initially mitoxantrone therapy at first, following two randomised trials that demonstrated a palliative benefit in symptomatic mCRPC without any survival improvement.23,24 Nowadays, mitoxantrone’s role is minimal, if present at all. Docetaxel (75 mg/m² every 3 weeks) plus daily oral prednisone (5 mg twice per day) is now considered the SoC for mCRPC requiring chemotherapy-based approaches in chemotherapy-naïve patients.8,25,26 This was established following the pivotal findings from a randomised clinical trial, the TAX-327 trial, in 1,006 men with mCRPC. Two docetaxel regimens (75 mg/m² every 3 weeks or 30 mg/m² weekly) were compared with mitoxantrone (12 mg/m² every 3 weeks).27 Both treatment arms also included prednisone therapy. The first schedule of docetaxel showed significant superiority over the second docetaxel schedule and mitoxantrone in terms of OS (19.2, 17.8, and 16.3 months, respectively) and 3-year survival rates, over a wide range of patients. PSA response was higher in the docetaxel treatment groups than in the mitoxantrone group, as was the QoL benefit.28

However, in this study, the 3-weekly docetaxel regimen was associated with higher occurrences of Grade 3 or 4 neutropaenia. In patients who do not tolerate a docetaxel regimen of 75 mg/m² every 3 weeks, docetaxel can be administered more frequently, as demonstrated by a randomised Phase III trial (NCT00255606) in 361 chemotherapy-naïve patients with mCRPC.29 Patients were randomly assigned to a schedule of 75 mg/m² every 3 weeks, or 50 mg/m² every 2 weeks. This regimen was associated with longer time to treatment failure and lower toxicity, namely Grade 3-4 events and neutropaenic infections. However, the size of the trial precludes this schedule to be considered the SoC.

In the elderly, the use of docetaxel either as a standard regimen (performance status 0 or 1) or an adapted regimen (performance status >2) was also explored. In 175 patients (aged 75 and older) docetaxel demonstrated additional benefits with an OS of 15 months and a median PFS of 7.4 months.30 Nevertheless, the recent recommendations from the International Society of Geriatric Oncology highlight the need to manage PrC according to each patient’s individual health status, not according to age.31

The SoC also changed from mitoxantrone plus prednisone to docetaxel therapy after the SWOG 99-16 study, in which docetaxel plus estramustine improved the median survival by 2 months when compared with mitoxantrone plus prednisone.32 In this Phase III trial, the former combination improved OS (17.5 months versus 15.6 months, p=0.02) with a corresponding HR for death of 0.80 (95% CI: 0.67-0.97). However, docetaxel plus estramustine was associated with substantial toxicity leading to estramustine no longer being used in combination with docetaxel. A number of clinical trials have evaluated the use of other agents as a combination therapy with docetaxel and prednisone, such as dasatinib,33 bevacizumab,34 or aflibercept,35 but all these combinations failed. Based on the difference between these two available taxanes, a Phase III clinical trial (the FIRSTANA study) is currently ongoing to evaluate and compare docetaxel with two doses of cabazitaxel as a first-line treatment in patients with mCRPC. This randomised, open-label, multicentre study (NCT01308567) aims to evaluate both compounds in terms of efficacy (OS, PFS), QoL, and safety.36

In second-line chemotherapy for mCRPC, the EAU does not suggest a definitive treatment strategy but highlights that cabazitaxel, abiraterone, enzalutamide, and radium-223 are effective in the
post-docetaxel setting. Docetaxel re-challenging could be suggested in the second-line setting following first-line docetaxel in well-responding patients with a relapse at least 3 months after stopping first-line docetaxel. It is unclear whether docetaxel still has a place given the availability of new compounds.37

**Cabazitaxel as a second-line chemotherapy agent**

Cabazitaxel is a novel microtubule-targeted, taxane-derived agent that has demonstrated important clinical anti-tumoural activity following docetaxel failure. As a consequence, cabazitaxel was approved as a second-line modality for CRPC requiring the use of chemotherapy in combination with prednisone in chemotherapy-experienced patients.38 Current EAU, AUA, and American Society of Clinical Oncology guidelines recommend cabazitaxel in relapsing patients with prior docetaxel therapy and good performance status.4,5,39 The TROPIC trial40,41 was the study supporting this treatment strategy, and which compared mitoxantrone plus prednisone with cabazitaxel plus prednisone in 755 men with CRPC progressing on docetaxel therapy. OS was improved in the cabazitaxel group (median survival of 15.1 and 12.7 months, respectively), as well as the PFS (2.8 and 1.4 months, respectively) and the 2-year OS rate (27% and 16%, respectively).

Nevertheless, cabazitaxel is associated with non-negligible toxicity, with 82% of patients experiencing Grade 3 or higher neutropaenia and 47% of patients experiencing diarrhoea (6% Grade 3 or higher). These adverse events can be effectively managed and even prevented if the patient is surrounded by an experienced team, as demonstrated by the real-life data published by Heidenreich et al.42 This is especially true for Grade 3-4 neutropaenia and diarrhoea.

An ongoing Phase III clinical trial (PROSELICA trial, NCT01308580) will certainly provide further efficacy, dosing, and safety data on the use of cabazitaxel plus prednisone in mCRPC patients previously treated with docetaxel.43 This randomised, open-label, multi-centre study will evaluate cabazitaxel 20 mg/m² versus cabazitaxel 25 mg/m² not only to determine the non-inferiority of cabazitaxel 20 mg/m² in terms of OS, but also to evaluate the safety profile, particularly the myelotoxicity, of both cabazitaxel regimens.

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**Table 1: Key Phase III clinical trials in metastatic castration-resistant prostate cancer.**

<table>
<thead>
<tr>
<th>Study</th>
<th>Agents</th>
<th>n</th>
<th>Indication</th>
<th>Inclusion criteria</th>
<th>HR</th>
<th>Δ OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAX-327²⁷</td>
<td>Docetaxel/prednisone vs. mitoxantrone/prednisone</td>
<td>1,006</td>
<td>mCRPC</td>
<td></td>
<td>0.76</td>
<td>+2.9</td>
</tr>
<tr>
<td>IMPACT²⁸</td>
<td>Sipuleucel-T vs. placebo</td>
<td>512</td>
<td>mCRPC</td>
<td>Asymptomatic (pre-docetaxel)</td>
<td>0.78</td>
<td>+4.1</td>
</tr>
<tr>
<td>COU-AA-302⁴⁶</td>
<td>Abiraterone/prednisone vs. prednisone</td>
<td>1,088</td>
<td>mCRPC</td>
<td>Asymptomatic/no visceral metastases</td>
<td>0.81</td>
<td>+4.4</td>
</tr>
<tr>
<td>COU-AA-301⁴⁴</td>
<td>Abiraterone/prednisone vs. prednisone</td>
<td>1,195</td>
<td>mCRPC</td>
<td></td>
<td>0.74</td>
<td>+4.6</td>
</tr>
<tr>
<td>PREVAIL⁴⁹</td>
<td>Enzalutamide vs. placebo</td>
<td>171</td>
<td>mCRPC</td>
<td>Asymptomatic/visceral metastases allowed (11%)</td>
<td>0.76</td>
<td>+4 (estimated)</td>
</tr>
<tr>
<td>AFFIRM⁵⁰</td>
<td>Enzalutamide vs. placebo</td>
<td>1,199</td>
<td>mCRPC</td>
<td></td>
<td>0.63</td>
<td>+4.8</td>
</tr>
<tr>
<td>TROPIC⁴⁰</td>
<td>Cabazitaxel/prednisone vs. mitoxantrone/prednisone</td>
<td>755</td>
<td>mCRPC</td>
<td></td>
<td>0.70</td>
<td>+2.4</td>
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<tr>
<td>ALSYMPCA²¹²²</td>
<td>Radium-223 vs. placebo</td>
<td>921</td>
<td>mCRPC</td>
<td>No visceral metastases</td>
<td>0.70</td>
<td>+2.8</td>
</tr>
</tbody>
</table>

mCRPC: metastatic castration-resistant prostate cancer; HR: hazard ratio; OS: overall survival.
Salvage hormonal therapy with novel agents

Abiraterone

Abiraterone acetate is a CYP17A1 inhibitor that inhibits the synthesis of testosterone at the adrenal level and plays a major role at the intracrine level by suppressing androgen synthesis in intraprostatic cells. It has to be used in conjunction with prednisone 10 mg daily. It has demonstrated significant benefits in OS in key Phase III trials, in both docetaxel-naïve and docetaxel-experienced mCRPC patients. In 1,195 mCRPC docetaxel-experienced patients, abiraterone plus prednisone significantly improved OS over placebo plus prednisone (median: 15.8 versus 11.2 months; HR: 0.74; 95% CI: 0.64-0.86), as well as time to PSA progression and radiographic PFS. Comparable results were observed in a Phase III trial in 1,088 chemotherapy-naïve patients who were randomised to either abiraterone plus prednisone or placebo plus prednisone. After a median follow-up of 49.2 months, abiraterone demonstrated significant and meaningful prolonged OS (median: 34.7 versus 30.3 months; HR: 0.81; 95% CI: 0.70-0.93).

Enzalutamide

Enzalutamide is an androgen receptor antagonist that demonstrated important clinical activity in CRPC. Its affinity for the androgen receptor is higher compared with the previously available antagonists, and it has a specific mode of action with the inhibition of receptor trafficking from the cytoplasm to the nucleus. In the AFFIRM trial, 1,199 docetaxel-experienced patients were randomised to receive enzalutamide or placebo. After a median follow-up of 14.4 months, improved median survival was observed in the enzalutamide group versus placebo (18.4 months versus 13.6 months), as well as improved PSA response, radiographic PFS, and QoL. The Phase III PREVAIL study aimed to evaluate the efficacy and safety of enzalutamide in 1,717 mCRPC patients who were chemotherapy-naïve. Median OS (risk of death; HR: 0.71; p<0.0001) was significantly higher in the enzalutamide arm compared with placebo. This trial led to an EMA indication extension for chemotherapy-naïve patients in October 2014. Updated results were presented at EAU 2015 based on 784 deaths. The overall results were confirmed (OS: HR: 0.77; 95% CI: 0.67-0.88; p=0.0002) and a 4-month improvement in median survival with enzalutamide (35.3 months [95% CI: 32.2 - not yet reached]) versus placebo (31.3 months [95% CI: 28.8-34.2]). After a median follow-up of 31 months, 52% of enzalutamide and 81% of placebo patients received ≥1 subsequent life-extending PrC therapies.

Other chemotherapy strategies beyond first and second-line

Given the lack of Phase III trial data, there is no current SoC for patients progressing on cabazitaxel therapy, and treatment modalities following taxane failure are limited, mostly based on limited Phase II cohorts at best. Third-line salvage strategies for taxane-refractory mCRPC include platinum-based regimens such as carboplatin, either in combination with docetaxel or paclitaxel. In Phase II clinical studies both regimens yielded further additional benefits, although modest, with median OS of 12.4 and 9.9 months, respectively. However, the available experience has been obtained before the availability of abiraterone, enzalutamide, or radium-223.

Oxaliplatin was also evaluated in three Phase II studies in heavily pre-treated CRPC patients, in combination with 5-fluorouracil, capecitabine, or pemetrexed. Median OS was 11.4, 5.5, and 11.9 months, respectively, with manageable toxicities. Cisplatin was also evaluated in combination with prednisone in 25 men who were refractive to docetaxel; 23% of patients with measurable disease displayed a partial response (median PFS: 6 months; OS: 55 weeks).

Emerging new agents in ongoing clinical trials

Emerging non-hormonal therapies that are currently being evaluated include novel immunotherapies such as sipuleucel-T - an autologous-registered and FDA-approved prostatic acid phosphatase, ProstVac-VF - a PSA-targeted poxviral-based vaccine, and nivolumab - an anti-PD1 antibody. Small molecule inhibitors such as custirsen are also currently being investigated in order to expand the therapeutic armamentarium for the remaining unmet needs in advanced PrC. Considering the lack of survival benefit, the development of tasquinimod was stopped, according to a press release April 16, 2015.

CONCLUSION

Contrary to many other malignancies, CC is still reserved for few clinical settings within PrC. These settings have been the subject of major clinical
research in past decades, since they represent important unmet needs. While abiraterone and enzalutamide were first evaluated in patients following failure of docetaxel, recent clinical data demonstrate improved OS and good safety profiles in chemotherapy-naive mCRPC for both new agents. Additionally, the indications for CC could be extended to selected ADT-naïve mPrC patients following the promising results of the CHAARTED trial on docetaxel combination therapy with ADT, which could very well challenge the current paradigm. However, uncertainty remains regarding the optimal target population, based on the conflicting results available. Long-term results from both these studies and ongoing trials will help further ascertain the role of chemotherapy in PrC, and will help refine the most appropriate treatment strategies for mPrC.

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