The evolution of chemotherapy for the treatment of prostate cancer

D. I. Quinn1*, H. M. Sandler2, L. G. Horvath3, A. Goldkorn1 & J. A. Eastham4

1Division of Medical Oncology, University of Southern California Norris Comprehensive Cancer Center, Los Angeles; 2Department of Radiation Oncology, Cedars-Sinai Medical Center, Los Angeles, USA; 3Department of Medical Oncology, Chris O’Brien Lifehouse and University of Sydney, Sydney, Australia; 4Urology Service, Memorial Sloan Kettering Cancer Center, New York, USA

*Correspondence to: Prof. David I. Quinn, Division of Medical Oncology, University of Southern California Norris Comprehensive Cancer Center, 1441 Eastlake Avenue, Suite 3440, Los Angeles, CA 90033, USA.
Tel: +1-323-865-3956; E-mail: diquinn@med.usc.edu

Chemotherapy has been explored as a treatment option for metastatic prostate cancer since the early 1980s. Docetaxel, a taxane chemotherapeutic, was approved for the treatment of men with metastatic castration-resistant prostate cancer in 2004, and is now standard of care for late stage disease. Recent clinical studies demonstrated that patients with metastatic castration-sensitive disease, and possibly those with high-risk localized prostate cancer also benefit from docetaxel administration, expanding the role of chemotherapy in the prostate cancer treatment landscape. Another taxane, cabazitaxel, is approved for post-docetaxel metastatic castration-resistant prostate cancer. Taxanes and other chemotherapeutics, such as carboplatin, are now being tested in combination regimens. This review presents an outline of recent and ongoing clinical studies assessing docetaxel and its derivative cabazitaxel at different stages of the disease, and in various combinations with other agents. We summarize current knowledge on biomarkers predictive of response to chemotherapy, which may in future be used to guide individualized treatment decisions.

Key words: prostate cancer, chemotherapy, taxane, sequencing, combination, biomarker

Introduction

Prostate cancer is one of the leading causes of cancer-related death in men worldwide [1]. Patients with early-stage prostate cancer can usually be managed with active surveillance, radiation or surgery. While most men with early-stage prostate cancer will not progress to advanced disease, in some cases clinically localized cancers can metastasize quickly despite local therapy; in addition, some men have metastatic disease at the time of prostate cancer diagnosis [2] (Figure 1). Localized prostate cancer is typically classified as high-risk based on prostate-specific antigen (PSA) levels, clinical stage and/or Gleason score [3]. Men with metastatic prostate cancer are at risk of substantial morbidity and mortality, hence treatment of localized high-risk disease has the potential to prevent development of metastases and improve survival. Metastatic prostate cancer can be castration-sensitive (mCSPC) or castration-resistant (mCRPC), with the majority of mCSPC cases eventually progressing to mCRPC after developing resistance to initial hormonal treatment [2] (Figure 1).

The first available chemotherapeutic options for patients with mCRPC, mitoxantrone and estramustine are now considered to be of little clinical benefit because neither agent has been shown to prolong overall survival (OS) [4–6] (Figure 2). Estramustine was approved for the treatment of mCRPC in 1981 based on small non-randomized studies showing improved rates of disease control over comparators [7, 8]. Estramustine adds to the toxicity of chemotherapy when given in combination, and while it may improve PSA response, it does not consistently improve OS [9–11]. Interestingly, a meta-analysis of 742 patients demonstrated better PSA response when given in combination, and while it may improve OS with the addition of estramustine to chemotherapy, but at the cost of significant adverse events [12]. Subsequently, in large phase III studies of docetaxel with estramustine (SWOG 9916) or without estramustine (TAX327), it was concluded that the benefit-to-risk ratio did not warrant routine use as a combination partner with docetaxel. Mitoxantrone was associated with significant palliative benefits and improved PSA response rates, which led to its approval in 1996 and subsequent establishment as standard of care [5–8].
In 2004, the taxane chemotherapy, docetaxel, replaced mitoxantrone as the standard of care following two phase III studies (TAX327 and SWOG 9916) in which docetaxel prolonged OS in patients with mCRPC [13, 14] (Figure 2). However, despite the efficacy benefits achieved with docetaxel-based treatment, approximately half of all patients do not respond, and those who do eventually develop resistance to docetaxel [13, 14]. Cabazitaxel, a second-generation taxane, was developed to overcome resistance to docetaxel, and has been shown to elicit clinical responses and provide improved OS, compared with mitoxantrone, when used post-docetaxel in patients with mCRPC (TROPIC phase III study [15]). Cabazitaxel was approved in 2010 for the treatment of patients with mCRPC who have previously received docetaxel-based regimens [7].
Subsequently, the mCRPC treatment landscape has been enriched with several other agents, including abiraterone, enzalutamide, sipuleucel-T and radium-223, which have been shown to improve survival and prolong time to disease progression in phase III studies (Table 1) [16–21]. All are now approved for the treatment of mCRPC (Figure 2) [22]. In addition, a recent phase II study (TOPARP-A) demonstrated that the PARP inhibitor olaparib has anti-cancer activity in patients with mCRPC, and response to treatment correlated with DNA-damage repair mutations in genes such as BRCA1, BRCA2 and ATM [23]. Some of the newer agents have partially overlapping mechanisms of action (Table 2), hence the question of how to optimize treatment sequence or combination therapies is becoming more and more pertinent.

With multiple classes of therapy now available for the treatment of mCRPC, where does chemotherapy fit within the prostate cancer treatment landscape? What data are available to guide decisions on combination therapy, drug sequencing and individualized treatment options, such as those guided by biomarkers? Here we review the evolving role of chemotherapy in the treatment of prostate cancer.
Metastatic castration-resistant prostate cancer

Docetaxel has a long-established position in the treatment paradigm for patients with mCRPC. In 2004, the TAX327 and SWOG 9916 studies showed that docetaxel-based regimens improve OS in patients with mCRPC when compared with mitoxantrone (Table 1), leading to the approval of docetaxel as a first-line treatment option for mCRPC [13, 14]. The National Comprehensive Cancer Network guidelines recommend docetaxel as a category 1 option for treatment of symptomatic mCRPC [22].

Cabazitaxel was developed to overcome resistance to docetaxel, and following positive results in the phase III TROPIC study, cabazitaxel was approved as a treatment option for mCRPC in men who progress on or after docetaxel-based regimens [15]. In TROPIC, patients with progressive post-docetaxel mCRPC receiving cabazitaxel had an improved median OS compared with patients receiving mitoxantrone (Table 1), suggesting cabazitaxel was active in the docetaxel-refractory disease setting [15].

More recently, cabazitaxel 25 and 20 mg/m\(^2\) (every 3 weeks) were compared with docetaxel in terms of OS in patients with chemotherapy-naïve mCRPC (FIRSTANA) [24]. No statistically significant differences between the three treatment groups were observed for OS or progression-free survival (PFS); therefore, the study did not demonstrate the superiority of cabazitaxel over docetaxel. Treatment with the cabazitaxel 20 mg/m\(^2\) dose resulted in a similar OS and less hematological toxicity than the 25 mg/m\(^2\) dose. The PROSELIKA study, which compared both doses of cabazitaxel to docetaxel, concluded that the 20 mg/m\(^2\) dose maintains at least 50% of the survival benefit observed in the TROPIC study, where cabazitaxel 25 mg/m\(^2\) was compared with mitoxantrone [15, 24, 25]. Of note, the PROSELIKA study reported lower toxicity for 20 mg/m\(^2\) than for 25 mg/m\(^2\) cabazitaxel dose with similar OS, suggesting that the dose may be reduced in patients who require it [25].

Docetaxel remains the approved chemotherapeutic option for patients with mCRPC who have not previously received chemotherapy [7, 22], although a case could be made for using first-line cabazitaxel in patients with precedent Grade 2 or greater sensory neuropathy.

A recent phase II study, TAXYNERGY, explored the extent of cross-resistance between taxanes by assessing the benefit of an early switch from docetaxel to cabazitaxel, and vice versa, in patients with mCRPC that did not respond to the initial treatment [26]. The results suggest that the cross-resistance may be limited, supporting other studies which demonstrated the benefit of cabazitaxel in patients who progressed on docetaxel-based therapy and preclinical data showing that cabazitaxel exerts antitumor activity in docetaxel-resistant cell lines [15, 27, 28].

With approval of radium-223 for mCRPC, the question has been raised whether prior radium-223 treatment may worsen the safety profile of subsequent chemotherapy. A recently reported exploratory analysis of patients with mCRPC receiving chemotherapy after radium-223 suggested that this sequence does not result in an increased toxicity profile [29]. Notably, the chemotherapy options assessed in this study did not include cabazitaxel; more information on the safety profile of cabazitaxel after radium-223 is needed.

Metastatic castration-sensitive prostate cancer

Combinations of chemotherapy and hormonal therapy were recently assessed in patients with mCSPC. Three phase III studies evaluated docetaxel combined with androgen deprivation therapy (ADT): CHAARTED [30, 31], STAMPEDE [32] and GETUG-AFU 15 [33], and all three studies were also evaluated in a meta-analysis [34].

In the CHAARTED study, patients with mCSPC were randomized to either ADT alone or ADT with six cycles of docetaxel [43]. The addition of docetaxel to ADT improved OS across the whole

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<th>Table 2. Mechanism of action of chemotherapy in prostate cancer</th>
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<td>AR dependence</td>
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<td>Non-taxane chemotherapies</td>
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<td>Taxanes</td>
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ADT, androgen deprivation therapy; AR, androgen receptor; mCRPC, metastatic castration-resistant prostate cancer.
group [Hazard Ratio 0.61; 95% confidence interval (CI), 0.47–0.80; P < 0.001], with most of the effect seen in high-volume metastatic prostate cancer. In STAMPEDE, patients with metastatic, high-risk locally advanced or high-risk relapsing prostate cancer who were starting first-line hormone therapy were administered hormonal therapy either alone, with zoledronic acid (ZA), with docetaxel or with both agents [32]. When administered at the time of hormonal therapy, docetaxel and docetaxel plus ZA demonstrated improved median OS compared with hormonal therapy alone (P = 0.006 and P = 0.022, respectively), whereas ZA alone did not (P = 0.450) [32]. However, GETUG-AFU 15 failed to demonstrate a significant OS benefit for docetaxel plus ADT versus ADT alone in patients with mCSPC, although it was noted that patients with high-volume disease may benefit more from docetaxel plus ADT versus ADT alone [33].

After long-term follow-up, the CHAARTED study confirmed that docetaxel plus ADT significantly improved OS in men with mCSPC compared with ADT alone (median OS: 58 versus 47 months; P = 0.0018), and the OS benefit appeared to be specific to patients with high-volume disease (defined as the presence of visceral metastases or ≥4 bone lesions with ≥1 beyond the vertebral bodies and pelvis) compared with low-volume disease (P < 0.0001 versus P = 0.86, respectively) [30, 31]. Of note, a subsequent CHAARTED quality-of-life analysis suggested that docetaxel treatment improves quality of life in patients with mCSPC after completion of chemotherapy [35]. The meta-analysis of all three studies showed that the combination of ADT plus docetaxel improved PFS and OS in patients with mCSPC, although it was noted that patients with high-volume disease may benefit more from docetaxel plus ADT versus ADT alone [33].

Localized prostate cancer

Although surgery and/or radiotherapy provide excellent disease control for early stages of prostate cancer, clinically localized high-risk disease is associated with a significant risk of recurrence after initial local therapy [2]. Several studies have evaluated the benefit of adjuvant and neoadjuvant chemotherapy for early stage disease. A phase III study that compared ADT plus radiotherapy and ADT plus radiotherapy plus adjuvant combination chemotherapy (estramustine, etoposide, paclitaxel and warfarin) in patients with high-risk localized prostate cancer (RTOG-9902) showed no clinical benefit for the adjuvant chemotherapy [36]. The study was closed early due to the excess toxicity of combination chemotherapy, primarily from the estramustine component. The SWOG S9921 phase III study also did not show any survival improvement for adjuvant ADT plus mitoxantrone plus prednisone compared with ADT alone in patients with high-risk localized prostate cancer [37]. Another study of adjuvant docetaxel in high-risk prostate cancer did not show a statistically significant improvement in PFS for the total population, but the results suggested a potential benefit for patients with higher risk pathology and African-American ancestry [38]. Earlier phase II studies that assessed docetaxel combinations with radical prostatectomy [39, 40], complete androgen blockade [41] and radiotherapy [42] showed that docetaxel is well tolerated in these settings and may improve recurrence-free survival.

Other phase III studies evaluated docetaxel in the adjuvant setting. The phase III study RTOG-0521 assessed the benefit of adding adjuvant docetaxel to external beam radiotherapy and androgen suppression for the treatment of high-risk localized prostate cancer [43]. Adjuvant chemotherapy improved 4-year OS, with a rate of 89% reported for ADT and radiotherapy alone versus 93% for ADT, radiotherapy and adjuvant docetaxel (one-sided P = 0.03) [43]. Conversely, the phase III SPCG12 study of adjuvant docetaxel following radical prostatectomy demonstrated that adjuvant docetaxel alone was not beneficial, in terms of biochemical-free survival, for patients with high-risk localized prostate cancer [44]. GETUG12, a phase III study of neoadjuvant docetaxel and estramustine added to ADT, suggested that docetaxel-based chemotherapy improves relapse-free survival in patients with high-risk localized prostate cancer, most of whom received radiotherapy as their primary treatment. After 8 years, the rate of relapse-free survival was 62% for patients receiving ADT plus docetaxel and estramustine versus 50% for patients receiving ADT alone (P = 0.017) [45]. An ongoing phase III study (NCIT00430183) is currently evaluating the benefit of neoadjuvant docetaxel plus luteinizing hormone-releasing hormone before surgery in high-risk localized disease [46]. Of note, a subset of patients with localized disease was included in the STAMPEDE study of docetaxel with or without ADT and/or ZA [32]. In this subgroup of patients, docetaxel-containing regimens did not significantly improve OS [32].

These results suggest that early use of chemotherapy in clinically localized, high-risk prostate cancer may provide clinical benefits; however, further studies and longer follow-up are needed to confirm an OS benefit. Improving outcomes in patients with high-risk localized prostate cancer remains an important therapeutic goal, and the integration of chemotherapies and other new treatments with current, established regimens used in early disease (such as ADT and radiotherapy) is an attractive therapeutic strategy.

Future use of chemotherapy in prostate cancer

The future use of chemotherapy in prostate cancer will be heavily influenced by a deep understanding of the molecular mechanisms driving treatment sensitivity or resistance in specific patient subsets. Chemotherapy-based treatment combinations and biomarker tests have the potential to direct individualized treatment.

Chemotherapy-based treatment combinations

The phenomenon of cross-resistance between chemotherapies and other treatments has been documented in preclinical and clinical studies of prostate cancer [47–49]; the degree of cross-resistance between individual agents varies and is likely to depend
on mechanism of action and individual patient predisposition [50, 51]. Cross-resistance has been observed between taxanes [docetaxel and cabazitaxel, which inhibit microtubule-dependent androgen receptor (AR) nuclear translocation] and AR- and CYP17-targeted agents (abiraterone and enzalutamide), possibly due to their partially overlapping mechanisms of action; however, this needs to be further explored [47]. For example, the degree of cross-resistance between docetaxel and abiraterone is unclear; some studies show reduced efficacy of docetaxel in patients who have received prior abiraterone [52, 53], whereas others suggest that docetaxel retains efficacy after prior abiraterone treatment [54, 55]. A recent study suggested that docetaxel maintains efficacy after prior abiraterone treatment [56]. With regard to cabazitaxel, prior abiraterone treatment does not appear to affect the subsequent antitumor activity of cabazitaxel [48, 49, 57–59]. The data on cross-resistance, however, are limited to serum PSA response and retrospectively assessed radiological non-progression, and further studies are warranted to help define the mechanisms of resistance and degree of cross resistance of such agents in order to optimize treatment sequencing for better patient outcomes.

Different approaches to overcome cross-resistance between chemotherapies and other therapeutic agents in the treatment of prostate cancer are being explored. One strategy is to administer treatments in combination rather than sequentially. A number of studies are currently evaluating different treatment combinations, including taxanes combined with ADT, AR-targeted therapy, other classes of chemotherapy and several other novel agents (Table 3). An ongoing phase III study (PEACE-1; NCT01957436) is assessing the benefits of coadministering docetaxel with ADT and abiraterone in patients with mCSPC [46]. Another large phase III study (PEACE-2; NCT01952223) is evaluating the combination of cabazitaxel with radiotherapy in patients with localized prostate cancer at high risk of relapse [60]. The results are eagerly awaited. The phase II ABIDO study is assessing the combination of docetaxel with abiraterone in patients with mCRPC who have progressed on prior abiraterone treatment; preliminary results suggest that the combination may have a worse safety profile than docetaxel alone [61]. The ongoing phase II CHEIRON study (NCT02453009) is evaluating the addition of enzalutamide to docetaxel in patients with mCRPC [46]. A phase II study of cabazitaxel plus abiraterone in patients with mCRPC after docetaxel treatment has

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<td><strong>Study name</strong></td>
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<td><strong>Phase III</strong></td>
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<td>PEACE-1 (NCT01957436)</td>
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<td>PEACE-2 (NCT01952223)</td>
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<td>VIABLE (NCT02111577)</td>
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<td>SYNERGY (NCT01188187)</td>
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<td>AFFINITY (NCT01578655)</td>
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ADT, androgen deprivation therapy; DCVAC, dendritic-cell immunotherapy vaccine; mCPRC, metastatic castration-resistant prostate cancer; OS, overall survival; PFS, progression-free survival; PSA, prostate-specific antigen.
demonstrated a manageable safety profile, a PSA response rate of 46% and a tumor response rate of 21% [62]. Further phase II studies of cabazitaxel in combination with abiraterone or enzalutamide in patients with mCRPC are currently ongoing (NCT01845792, NCT02218606, NCT02522715) [46].

Docetaxel is also being evaluated in combination with the autologous dendritic-cell immunotherapy vaccine DCVAC. DCVAC comprises monocyte-derived dendritic cells pulsed with prostate cancer cells that are destroyed by high hydrostatic pressure (immunogenic destruction) [63, 64]. A phase I/II study of a DCVAC–docetaxel combination in patients with mCRPC eligible to receive docetaxel reported a favorable safety profile, and patients survived longer than predicted [64]. A large phase III study is currently assessing DCVAC in combination with docetaxel in patients with mCRPC (NCT02111577) [65].

Both docetaxel and cabazitaxel have been assessed in combination with custirsen, a second-generation antisense inhibitor of the protein clusterin, which may play a role in cancer cell survival and treatment resistance [66]. Unfortunately, both combinations failed to show a survival benefit for patients with mCRPC in phase III studies (SYNERGY [67] and AFFINITY [68]). Subgroup analyses of the SYNERGY study suggested that patients with a poor prognosis might benefit from the addition of custirsen to docetaxel treatment [67]. However, the AFFINITY study showed no survival benefit in patients receiving post-docetaxel custirsen plus cabazitaxel compared with cabazitaxel alone [69].

Combinations of platinum-based chemotherapy with taxane chemotherapy were expected to avoid cross-resistance and increase clinical efficacy due to the differing mechanisms of action [50]. Two early phase II studies assessed the combination of docetaxel, carboplatin and estramustine [70], and docetaxel and carboplatin [71] in patients with mCRPC. A PSA response rate of 68%, a tumor response rate of 52% and a median OS of 19 months was observed in patients receiving docetaxel, carboplatin and estramustine [70]; the respective data for patients receiving docetaxel and carboplatin only were 18%, 14% and 12.4 months [71]. The docetaxel, carboplatin and estramustine study concluded that the triplet combination had significant clinical activity with an acceptable safety profile, while the docetaxel and carboplatin combination study showed modest clinical activity; both combinations warrant further assessment [70, 71]. A randomized phase II study of cabazitaxel with or without carboplatin in patients with mCRPC showed an improvement in PFS (median 7.4 versus 4.6 months; P = 0.004), and PSA and tumor response rates, compared with cabazitaxel alone; this efficacy benefit was accentuated in patients meeting the spectrum of clinical criteria of the aggressive variant disease [72]. Rates of commonly reported adverse events were increased in the combination arm [72]. A confirmatory phase III study is needed to determine whether this chemotherapy combination is a viable treatment option for patients with mCRPC. Of note, the combination of docetaxel plus carboplatin is being evaluated in a phase II study that includes patients with mCRPC with mutations in BRCA1/2 pathway [46].

Biomarkers

The concept of disease heterogeneity and personalized medicine has only recently been applied in the treatment of disseminated prostate cancer. Thus, there is an urgent need to identify the most informative biomarkers that can predict a patients’ sensitivity or likelihood of developing resistance, to available therapies. Several candidate biomarkers are currently being evaluated in metastatic disease.

Prostate cancer, like other solid malignancies, is characterized by the shedding of cells from the primary tumor into circulation, and these circulating tumor cells (CTCs) ultimately result in seeding and growth of metastases [73]. Identification, enumeration and molecular analysis of CTCs may help to detect early systemic disease and facilitate the analysis of an individual patient’s tumor profile. CTC analysis is yet to be proven clinically useful in the context of localized prostate cancer. Initial studies suggested that CTC numbers do not correlate with risk of metastases [74], although higher CTC levels may be indicative of early tumor dissemination in some patients [75]. In mCSPC and mCRPC, CTC numbers at baseline and changes in CTC levels during ADT treatment have been shown to have prognostic value [76, 77]. Furthermore, baseline CTC numbers have been shown to predict response rate and duration of response to ADT in mCSPC [76–79]. In mCRPC, both initial CTC number [80] and an increase in the number of CTCs in patients receiving chemotherapy or abiraterone therapy is associated with OS [81–83]. It has been proposed that CTC enumeration should be included in predictive factor panels [83]. A meta-analysis of published literature further supports the prognostic value of CTCs, with findings suggesting that increased CTC/disseminated tumor cell numbers are predictive of poor prognosis (OS and biochemical relapse-free survival or disease-free survival) in both mCRPC and localized prostate cancer [84].

Although a number of studies assessing CTCs in high-risk localized prostate cancer did not observe a correlation between CTC count and biochemical recurrence of the disease, it was suggested that detailed CTC phenotyping may be useful [85]. CTC analysis provides a non-invasive approach to screen individual patients for molecular markers that are characteristic of individual tumors. Furthermore, proof of principle whole genome and whole exome sequencing of CTCs derived from prostate cancer patients has shown that a proportion of mutations in CTCs can be traced back to the tumor tissue [86, 87]. A study that applied RNA sequencing to single CTCs reported alterations in the AR and Wnt signaling pathways in CTCs from patients progressing on enzalutamide treatment, suggesting that tumor and CTC heterogeneity might contribute to resistance to enzalutamide [88]. CTC markers which may be predictive of response/progression, or resistance to particular treatments include telomerase activity [89], presence of AR splice variant 7 (ARv7) [90], AR signaling aberrations [91] and changes in AR nuclear localization in response to treatment [26, 92–94].

There are currently no confirmed biomarkers that can predict sensitivity or resistance to chemotherapy in prostate cancer, although several candidates are under investigation (Table 4). A potential predictive marker for response to chemotherapy in prostate cancer is overexpression of the E26 transformation-specific regulated gene (ERG), which has been linked to decreased taxane sensitivity, possibly due to ERG interfering with taxane-microtubule binding [95]. ERG overexpression is often the result of ERG fusion with the androgen-regulated gene TMPRSS2, which is present in 40%–80% of prostate cancers [96]. ERG gene
rarrangement is frequently detected in CTCs and may have potential as a marker of advanced disease; however, current data are contradictory as to its relationship to taxane sensitivity [97–99]. The TAXYNERGY study assessed predictive biomarkers of response to docetaxel and cabazitaxel, and found that response to treatment was correlated with AR nuclear localization in CTCs [26]. This suggests that assessment of AR status in CTCs may be a useful marker of taxane sensitivity/resistance. AR-V7 status and CTC heterogeneity can additively identify patients who are more likely to have worse outcomes with AR-targeted therapy relative to taxane treatment; thus, patients with high CTC heterogeneity and expression of the AR-V7 splice variant may derive more benefit from taxane treatment than AR-targeted agents [100, 101].

Plasma cell-free DNA (cfDNA) has also been investigated as a potential source of information for tumor mutation status and as a predictor of treatment response. Two studies, which analyzed cfDNA derived from patients with mCRPC, showed that AR gene aberrations in cfDNA are associated with resistance to abiraterone or enzalutamide [102, 103]. Another study assessing the cfDNA mutational status in 43 patients with metastatic disease showed that oncogenic mutations were not only present in the vast majority of patients, but also changed during treatment in 40% of cases. The authors suggested that the cfDNA mutational status changes under selective pressure in some cases, i.e. when a specific treatment is administered [104]. It has been suggested that a higher level of cfDNA at baseline is associated with advancing disease and poorer prognosis, and may predict worse OS and PFS in patients receiving taxanes; next-generation sequencing is ongoing in this study [105].

In vitro studies suggest that resistance to docetaxel may, in part, be mediated by cytokines induced via the interaction of docetaxel-resistant tumor cells with macrophages; anti-inflammatory cytokines such as MIC1 inhibit the antitumor inflammatory response [106]. In accordance with preclinical data, the baseline level of cytokines (in particular MIC1) was an independent predictor of OS, suggesting that increased levels of circulating cytokines are associated with docetaxel resistance in CRPC [106].

Other markers associated with response to chemotherapy and/or survival include methylated DNA in the promoter region of the GSTP1 gene, which encodes the glutathione S-transferase P enzyme and is inactivated in 90% of prostate cancers [107–109], and blood levels of several microRNAs (miRNAs) [110]. In the clinic, elevated levels of miR-200 family members are associated with very high-risk prostate cancer [111], and also associated with resistance to docetaxel and poorer OS in patients with mCRPC [110].

### Table 4. Overview of prognostic/predictive biomarkers relevant to chemotherapy in prostate cancer

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<th>Marker</th>
<th>Results</th>
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<td>Localized disease: no correlation with risk of recurrence</td>
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<td>A sign of early tumor dissemination</td>
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<td>mCSPC: predict response to ADT</td>
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<td>mCRPC: baseline levels predict survival during chemotherapy treatment</td>
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<td>mCRPC: changes in CTC numbers predict OS during chemotherapy treatment</td>
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<td>mCRPC: changes in CTC numbers predict OS during post-docetaxel abiraterone treatment</td>
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<td><strong>Blood/plasma markers</strong></td>
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<tr>
<td>Plasma-free circulating DNA levels</td>
<td>Correlation with OS and PFS during chemotherapy treatment</td>
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<tr>
<td>miRNA</td>
<td>Correlation with PSA response during docetaxel treatment</td>
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<tr>
<td>Cytokines</td>
<td>Predictive of taxane resistance</td>
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<td><strong>Intracellular markers</strong></td>
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<tr>
<td>% of CD133 and E-cadherin-positive CTC</td>
<td>Predict biochemcial recurrence after surgery</td>
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<tr>
<td>Telomerase activity</td>
<td>Higher baseline levels correlate with poorer OS outcomes during docetaxel treatment</td>
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<td>AR nuclear localization</td>
<td>Correlation with response to taxanes</td>
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<td>AR signaling; Wnt signaling</td>
<td>Wnt signaling activation correlates with treatment resistance to androgen receptor inhibitor</td>
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<td>ERG</td>
<td>Predictive of taxane resistance</td>
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<td><strong>Gene expression</strong></td>
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<td>Gene expression signatures</td>
<td>CTC heterogeneity (based on single cell profiling) could contribute to treatment failure</td>
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<td>Whole blood genomic profiling may help stratify patients into distinct prognostic groups</td>
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<td><strong>Non-invasive exosomal assays designed to assess disease burden</strong></td>
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<td>Exosomal miRNA</td>
<td>Plasma expression levels of certain miRNA are associated with OS and might be prognostic of CRPC</td>
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<tr>
<td>Exosomal proteins</td>
<td>Certain proteins found in urinary exosomes may be used for non-invasive diagnostics of prostate cancer</td>
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<td>Exosomal gene expression</td>
<td>Gene expression analysis of urinary exosomes may discriminate high-grade and low-grade cancer from benign tumors</td>
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AR, androgen receptor; CTC, circulating tumor cell; CRPC, castration-resistant prostate cancer; ERG, E26 transformation-specific-regulated gene; OS, overall survival; PFS, progression-free survival; PSA, prostate-specific antigen.
Other studies suggest that whole-blood gene expression profiling could identify expression signatures which stratify patients with CRPC into distinct prognostic groups [112–114]. These findings prompted the initiation of the prospective multicenter biomarker study PROSTAC (NCT02362620), which will validate the prognostic value of a previously characterized nine-gene expression signature in patients with CRPC who are eligible to receive docetaxel or cabazitaxel [112].

Taken together, several biomarkers which may inform treatment decisions in prostate cancer have been identified and show promise, including CTCs, AR splice variants, specific genetic alterations, cytokines and miRNA; however, these require further validation. Ongoing expression profiling studies for large cohorts of patients will be instrumental in finding the most clinically relevant biomarkers to predict response to treatment in patients with prostate cancer.

Discussion

Conclusions

Several approved treatments are currently available to treat patients with mCRPC, and the treatment paradigm is constantly evolving. Historically, chemotherapies provided only palliative benefit for patients with mCRPC, but after demonstrating improved survival, docetaxel was approved and became the standard of care for patients with mCRPC. Today, taxane chemotherapies recommended as treatment options for patients with mCRPC include docetaxel and cabazitaxel, the latter being approved for post-docetaxel use. Initially used in the context of mCRPC, chemotherapeutic regimens are now being explored and utilized in earlier stages of prostate cancer, such as high-risk localized disease and mCSPC, and in adjuvant/neoadjuvant settings with other treatments or surgery. Recent evidence suggests that docetaxel should be considered in men with high volume or ‘de novo’ metastatic disease starting ADT who can tolerate docetaxel chemotherapy. Several ongoing studies are exploring how chemotherapy can be optimized for the treatment of prostate cancer by assessing various treatment sequences and treatment combinations across all stages of the disease. Finally, clinical and laboratory data suggest that several biomarkers may be useful in predicting response and/or resistance to chemotherapy in order to identify patients who may or may not benefit from chemotherapeutics or other agents (Figure 1). The use of chemotherapy in prostate cancer has evolved enormously since its introduction ~30 years ago, and in future, routine biomarker assessment may help to validate its utility in individualized treatment.

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