Review Article

Chemotherapy options in castration-resistant prostate cancer

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ABSTRACT

Introduction: The treatment landscape for patients with metastatic castration-resistant prostate cancer (CRPC) is evolving, with recent approvals of immune therapy, novel hormonal therapy, and bone-targeted therapy. Chemotherapy remains an essential component of the armamentarium. Herein, we review current chemotherapy options for patients with CRPC and discuss future challenges.

Methods: We reviewed literature for chemotherapy agents in prostate cancer, with special attention to the evidence for efficacy of the currently approved agents. We also reviewed emerging data on biomarkers of response to chemotherapy for CRPC.

Results: Taxanes, especially docetaxel and cabazitaxel, have first- and second-line indications for CRPC, respectively, with both providing a survival benefit. Multiple attempts to improve on the single agent efficacy of docetaxel with combination therapy have not generally been successful although platinum combinations are used for resistant phenotypes. Reductions in prostate-specific antigen by ≥30% and reductions in circulating tumor cells (CTCs) to ≤ 5 are associated with improved survival on chemotherapy. Chemotherapy may continue to be effective therapy for patients with biomarkers that are associated with resistance to androgen-directed therapies (androgen receptor splice variant 7 positivity in CTCs or high CTC heterogeneity).

Conclusions: Chemotherapy remains an essential component of CRPC therapy, and biomarkers are being identified to define clinical scenarios where chemotherapy may be the optimal therapy choice.

Key words: Biomarkers, chemotherapy, prostate cancer

INTRODUCTION

The treatment options available for patients with metastatic castration-resistant prostate cancer (CRPC) have vastly expanded in recent years. Chemotherapy, especially docetaxel, was the first therapy that demonstrated a survival benefit for these patients.[1] So far, the field seemed to be moving away from chemotherapy as the mainstay of therapy for patients as novel hormonal therapies were introduced. The novel hormonal agents (abiraterone, enzalutamide, and many other experimental agents under active investigation) have rapidly moved to up-front treatment for CRPC.[2,3] However, there is now a renewed interest in defining the role of chemotherapy in patients with CRPC for several reasons. First, studies of chemotherapy plus androgen deprivation therapy (ADT) in castration-sensitive disease have demonstrated substantial survival advantages compared to ADT alone.[4,5] Second, sequential treatment with novel hormonal agents in CRPC has been hampered by cross-resistance,[6] and chemotherapy is emerging as a therapy that potentially retains efficacy after the development of resistance to hormone therapies.

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Access this article online	
Quick Response Code:	Website: www.indianjurol.com
	DOI: 10.4103/0970-1591.191239

How to cite this article: Teply BA, Hauke RJ. Chemotherapy options in castration-resistant prostate cancer. Indian J Urol 2016;32:262-70.

In the course of this review, we will discuss the Food and Drug Administration (FDA)-approved chemotherapeutics for castrate-resistant prostate cancer, including estramustine, mitoxantrone, docetaxel, and cabazitaxel. We will also discuss chemotherapeutics listed in the National Comprehensive Cancer Network (NCCN) compendium for prostate cancer, but are not FDA-approved specifically for the indication, including cisplatin, carboplatin, and etoposide, as well as discuss emerging data for potentially predictive or prognostic biomarkers for response to chemotherapy.

TAXANES: THE CORNERSTONE FOR CHEMOTHERAPY FOR CRPC

Docetaxel

Docetaxel was FDA-approved in 2004 for its ability to prolong survival in patients with metastatic CRPC. In fact, it was the only life-prolonging therapy available from its approval in 2004 through 2010, and further drug development during this time was defined in either pre- or post-docetaxel therapy context. Docetaxel is a semisynthetic taxane chemotherapeutic whose cytotoxic mechanism of action occurs through binding microtubules to prevent depolymerization, arresting the cell cycle and eventually resulting in apoptosis. Specifically for prostate cancer, docetaxel is also believed to interfere with androgen receptor (AR) trafficking, which relies on microtubule machinery.[7]

Two pivotal trials demonstrating a survival benefit for docetaxel were published in 2004. The first of these trials, TAX327, was a randomized Phase III trial performed in 1006 patients comparing the prior standard of care (mitoxantrone) with two dosing schedules of docetaxel (75 mg/m^2 every 3 weeks and 30 mg/m^2 weekly, for up to ten cycles).[1] All arms in the study received prednisone 5 mg twice daily. The cohort receiving docetaxel every 3 weeks had superior overall survival compared to mitoxantrone (18.9 vs. 16.5 months, hazard ratio [HR] =0.76, P = 0.009). No evidence of improved outcomes or decreased adverse events was found with weekly docetaxel. The trial also demonstrated superior quality of life (23% vs. 13%, P = 0.005) and improvement in pain (31% vs. 22%, P = 0.08) for docetaxel compared to mitoxantrone. Demonstrating both palliative and overall survival benefits was important for the study as the prior approval for mitoxantrone plus prednisone was based on palliative metrics.[8]

The second trial (Southwest Oncology Group [SWOG] 9916) that demonstrated a survival benefit for docetaxel in comparison with mitoxantrone studied the combination of docetaxel with estramustine.[9] Mitoxantrone and estramustine had previously been the only approved chemotherapeutics for prostate cancer. In this Phase III trial performed in 674 patients, docetaxel 60 mg/m^2 on day one plus estramustine 280 mg three times daily on days 1–5 of a 21-day cycle was compared with mitoxantrone plus prednisone. The docetaxel plus estramustine cohort had a superior overall survival (17.5 vs. 15.6 months, HR = 0.80, P = 0.02). However, a follow-up study of docetaxel plus prednisone with or without estramustine failed to demonstrate a clinical benefit with the addition of estramustine.[10] Every three week docetaxel plus prednisone was adopted as the standard of care and remains the first-line chemotherapy of choice for metastatic CRPC. While prednisone is sometimes omitted from the regimen in contemporary practice, it likely contributes to the efficacy[11] and/or tolerability[12] of docetaxel.

Subsequent work sought to increase the efficacy of docetaxel through a series of clinical trials that added agents to the docetaxel plus prednisone regimen. Unfortunately, none of these approaches was able to demonstrate a clinically significant additive benefit, and single-agent sequential therapy has remained the standard approach for patients. Agents that were tried in combination with docetaxel plus prednisone included anti-angiogenesis agents, immunomodulatory agents, tyrosine kinase inhibitors, and vitamins, among others. Table 1 summarizes selected placebo-controlled Phase II or III trials with experimental agents added to docetaxel.

While docetaxel was initially used for metastatic CRPC, recent data are leading to a paradigm shift regarding the timing of its use. After docetaxel had been shown to be effective in metastatic CRPC, several large trials were undertaken to test the hypothesis about whether there was a benefit to up-front chemotherapy after the initial diagnosis of castration-sensitive prostate cancer. The first reported trial (Groupe d'Etude des Tumeurs Uro-Genital - Association Française d'Urologie [GETUG- AFU]-15) reported no improvement in survival outcomes for the addition of up to nine cycles of docetaxel to standard ADT (58.9 vs. 54.2 months, HR = 1.01, P = 0.96).[37] However, two subsequently reported trials with similar designs demonstrated significant benefits with the addition of docetaxel. In CHAARTED, patients receiving ADT plus up to six cycles of docetaxel had a 13.6-month median overall survival benefit compared to the patients receiving ADT alone (57.6 vs. 44.0 months, HR = 0.61, P < 0.001).[5] In STAMPEDE, the cohort receiving ADT plus up to six cycles of docetaxel plus prednisone showed a 10-month median overall survival advantage compared to ADT alone (81 vs. 71 months, HR = 0.78, P = 0.006).[4] Given the conflicting results between the GETUG-AFU-15 trial and the subsequent CHAARTED and STAMPEDE trials, a meta-analysis was recently performed. In that analysis of the 2262 patients with metastatic disease from those three trials, docetaxel plus ADT resulted in improved survival compared to ADT alone (HR = 0.73, P = 0.002).[38]

In the future, patients are increasingly likely to have received docetaxel for hormone-sensitive disease. Further work is needed to define the best treatment strategies for

Table 1: Randomized clinical trials of docetaxel plus experimental agents in castration-resistant prostate cancer

Agent tested	*n*	Endpoint	Result	Publication year [references]
Docetaxel/prednisone ± lenalidomide	1059	OS	Inferior OS (17.7 vs. NR, *P*<0.01)	2015[13]
Docetaxel/prednisone ± cyclophosphamide	33	PSA RR	No difference	2015[14]
Docetaxel/prednisone ± figitumumab	204	PSA RR	No difference (52 vs. 60%, *P*=0.13)	2014[15]
Docetaxel/prednisone ± zoledronic acid	105	PFS*	Superior PFS (9.0 vs. 6.0 months, *P*<0.05)	2014[16]
Docetaxel/prednisone ± dasatinib	1522	OS	No difference (21.5 vs. 21.2 months, *P*=0.9)	2013[17]
Docetaxel/prednisone ± aflibercept	1224	OS	No difference (22.1 vs. 21.2 months, *P*=0.38)	2013[18]
Docetaxel/prednisone ± atrasentan	994	OS*	No difference (17.8 vs. 17.6 months, *P*=0.64)	2013[19]
Docetaxel/prednisone ± zibotentan	1052	OS	No difference (20.0 vs. 19.2 months, *P*=0.96)	2013[20]
Docetaxel/prednisone ± LY2181308	154	PFS	No difference (8.6 vs. 9.0 months, *P*=0.76)	2013[21]
Docetaxel/prednisone ± intetumumab	131	PFS	Inferior PFS (7.6 vs. 11.0 months, *P*=0.02)	2013[22]
Docetaxel/prednisone ± enzastaurin	94	RR	No difference (15.0 vs. 15.2%, *P*=1.00)	2013[23]
Docetaxel ± MVA-5T4	25	PFS	No difference (9.7 vs. 5.1 months, *P*=0.10)	2013[24]
Docetaxel/prednisone ± bevacizumab	1050	OS	No difference (22.6 vs. 21.5 months, *P*=0.18)	2012[25]
Docetaxel/prednisone ± risedronate	592	PFS	No difference (6.5 vs. 7.0 months, *P*=0.75)	2012[26]
Docetaxel/prednisone versus docetaxel/calcitriol	953	OS	Inferior OS (17.8 vs. 20.2 months, *P*=0.002)	2011[27]
Docetaxel/prednisone ± AT-101	221	OS	No difference (18.1 vs. 17.8 months, *P*=0.63)	2011[28]
Docetaxel/prednisone versus docetaxel/epirubicin	72	PFS	Superior PFS (11.1 vs. 7.7 months, *P*<0.01)	2011[29]
Docetaxel ± vadimezan	74	PFS*	No difference (8.7 vs. 8.4 months, NS)	2010[30]
Docetaxel/prednisone ± custirsen	82	PSA RR	No difference (58 vs. 54%, NS)	2010[31]
Docetaxel ± oblimersen	111	PSA RR	No difference (37 vs. 46%, NS)	2009[32]
Docetaxel/prednisone ± vandetanib	86	PSA RR	No difference (40 vs. 67%, *P*=0.99)	2009[33]
Docetaxel/prednisone ± estramustine	150	PSA RR	No difference (73 vs. 69%, NS)	2008[10]
Docetaxel ± doxercalciferol	70	PSA RR	No difference (46.7 vs. 39.4%, *P*=0.56)	2008[34]
Docetaxel ± imatinib	116	PFS	No difference (4.2 vs. 4.2 months, *P*=0.58)	2007[35]
Docetaxel ± thalidomide	75	PFS*	No difference (5.9 vs. 3.7 months, *P*=0.32)	2004[36]

*A composite primary endpoint was employed in the trial; one of the endpoints has been selected to be reported here. OS=Overall survival, RR=Response rate, PFS=Progression-free survival, NR=Not reached, NS=Not significant

these patients with metastatic CRPC with prior docetaxel treatment. For these patients, the outstanding questions include defining the role for docetaxel rechallenge versus second-line chemotherapy, and the optimal timing for incorporation of sipuleucel-T or other emerging immunotherapy approaches.

Cabazitaxel

Like docetaxel, cabazitaxel is a semisynthetic taxane chemotherapeutic that prolongs survival in metastatic CRPC. Although docetaxel and cabazitaxel share common mechanisms of action, cabazitaxel has less affinity for multidrug resistance proteins including the P-glycoprotein efflux pump.[39] Cabazitaxel retained activity in preclinical models of prostate cancer that were resistant to docetaxel, and thus cabazitaxel was formally studied in clinical trials in CRPC. The registrational TROPIC trial for cabazitaxel had a similar design to TAX327 wherein 775 patients were randomized to receive either cabazitaxel 25 mg/m^2 every 3 weeks or mitoxantrone every 3 weeks for up to ten cycles.[40] Both arms received 10 mg of prednisone daily along with the chemotherapy. Patients receiving cabazitaxel plus prednisone had superior median overall survival (15.1 vs. 12.7 months, HR = 0.7, $P < 0.0001$). Based on these data, cabazitaxel was FDA-approved in 2010 for patients with CRPC who previously had received docetaxel.

Cabazitaxel is dose-limited by neutropenia, similarly to docetaxel. Grade 3 or higher neutropenia was common (82%) among the cabazitaxel-treated patients, including an 8% incidence of febrile neutropenia. Neuropathy was uncommon with cabazitaxel, which is an important difference between the toxicity profile between docetaxel and cabazitaxel. In the TROPIC study, only 1% of patients developed Grade 3 peripheral neuropathy, with 14% rate of all grades of peripheral neuropathy. The low rate of neuropathy with cabazitaxel is an important aspect of its treatment, especially in the postdocetaxel setting where patients may already

have some degree of chemotherapy-induced peripheral neuropathy.

While cabazitaxel is currently approved only for docetaxel-pretreated patients with CRPC, ongoing trials are testing cabazitaxel as first-line therapy or in combination with other active agents. The Phase III FIRSTANA trial (NCT01308567) tested two dosing regimens of the first-line cabazitaxel plus prednisone versus docetaxel plus prednisone with a primary endpoint of overall survival.[41] While cabazitaxel has been studied at 25 mg/m^2, 20 mg/m^2 dose is potentially equally efficacious but more tolerable. Cohorts for both dosing strategies are included in the FIRSTANA trial. The presentation of the data in abstract form suggests that survival outcomes for first-line docetaxel and cabazitaxel were similar.[42] Similarly, as docetaxel was studied with other agents in an attempt to improve outcomes, there are ongoing trials with cabazitaxel in combination with other drugs. These pending studies include combinations of cabazitaxel with novel hormonal agents, including abiraterone or enzalutamide, as well as targeted agents.

PALLIATIVE THIRD LINE (AND BEYOND) AGENTS

The NCCN compendia currently list only three chemotherapeutic agents (docetaxel, cabazitaxel, and mitoxantrone) for pure adenocarcinoma of the prostate, all of which carry FDA indications for metastatic CRPC. These drugs have demonstrated a benefit in clinical trials, yet others have also been used palliatively in prostate cancer. Estramustine was previously FDA-approved agent for treatment of CRPC, before the development of newer, more effective agents. Cyclophosphamide, broadly approved for the treatment of cancer in 1959, was used in a variety of malignancies including CRPC, before the advent of newer agents.

Mitoxantrone

Mitoxantrone is cytotoxic by intercalating into DNA and inhibiting topoisomerase II. The trial that led to mitoxantrone's FDA-approval randomized 161 patients with symptomatic CRPC to either mitoxantrone 12 mg/m^2 every 3 weeks plus prednisone 10 mg daily or prednisone alone.[8] The primary endpoint of the study was reduction in pain; therefore, all patients who were admitted to the study were required to have pain. Mitoxantrone plus prednisone was more effective in reducing pain, with 29% (18/80) of patients meeting the endpoint of a two-point reduction on a 6-point pain scale, maintained over at least 3 weeks. Prednisone alone only achieved pain reduction in 12% (10/81) of patients ($P = 0.01$). Crossover was allowed on the trial; palliation of pain as a primary endpoint was met but no differences in overall survival were seen. The treatment was generally well tolerated, but authors noted that five patients of the 130 total that received the anthracenedione (thus including the crossover patients) developed cardiac abnormalities. Despite the protocol intention to cap the total mitoxantrone dose at 140 mg/m^2, most of the patients who developed the cardiac abnormalities received higher cumulative doses than the protocol called for.

While mitoxantrone remains an available option for patients with symptomatic CRPC, the emergence of taxanes has led to infrequent modern use of mitoxantrone. Docetaxel plus prednisone demonstrated superior quality of life and pain outcomes in TAX327, and cabazitaxel plus prednisone achieved similar palliative outcomes in TROPIC, both while extending overall survival. Mitoxantrone may still be used for palliative purposes for patients after progression on the life-prolonging taxanes. However, it is important to note that the data demonstrating efficacy of mitoxantrone plus prednisone were for chemotherapy-naïve patients. We are not aware of any data reaffirming palliative efficacy of mitoxantrone after cabazitaxel treatment although it remains a reasonable option for symptomatic patients for whom other treatment options are exhausted.

Estramustine

Although estramustine is listed here as chemotherapeutic, it likely acts through several mechanisms (including hormonally) to be efficacious in CRPC. Estramustine is a small molecule that is an estrogen mimetic combined with a nitrogen mustard. It binds microtubules to have cytotoxic effects. Long-term use of estramustine, which must be dosed up to four times daily, results in elevated estrogen levels. Side effects are mainly gastrointestinal, but hormonally related effects are also seen.

Estramustine was FDA-approved in 1981 for clinical responses in prostate cancer.[43] In the trials, estramustine treatment resulted in objective tumor responses and improvement in pain. It was an available option for patients, and estramustine was postulated to potentially be synergistic with other therapies. Thus, further trials attempted to incorporate estramustine as part of combination therapy. As mentioned in the discussion with docetaxel, estramustine was combined with docetaxel in one of two pivotal trials demonstrating a survival benefit for the combination in comparison with mitoxantrone. The potential synergy of adding estramustine to docetaxel and prednisone was tested in a Phase III trial, wherein 150 patients with CRPC were randomized to receive docetaxel plus prednisone with or without estramustine 280 mg three times daily on days 1–5 and 8–12 of a 21-day cycle.[10] Severe adverse events were increased with the addition of the estramustine (grade 3–4 toxicity of 45% vs. 21%), and there were no significant differences in responses or survival.

Although it has been periodically tested in combination with other agents since that time, its use has largely fallen out of favor with the expanding options now available for the treatment.

Cyclophosphamide

Oral cyclophosphamide was commonly used in men with CRPC before the availability of the newer agents. The ability to deliver the well-tolerated therapy orally at home led to its investigation for use in CRPC. Cyclophosphamide has been studied as both a single agent or in combination. Small studies of cyclophosphamide have mostly been single-arm studies and reported benefits have been modest.[44] More recent efforts have focused on low-dose metronomic cyclophosphamide,[45] which potentially is effective as a chemotherapeutic to enhance immunity and inhibit angiogenesis.[46] PSA, objective and palliative responses have been reported with a variety of dosing regimens and combinations (including with corticosteroids); however, no high-level evidence to justify its use as a standard of care is available. Yet, the tolerability and ease of administration (orally at home) make cyclophosphamide an option for appropriate CRPC patients.

PLATINUM COMBINATION CHEMOTHERAPY

Platinum-taxane combinations for progressive CRPC

Platinum-taxane combinations have been used as second-line therapy for docetaxel-refractory CRPC, especially before the introduction of cabazitaxel. Platinum agents were tested in the past for prostate cancer, and some subsequent studies looked into platinum combinations, both as first- and second-line chemotherapy. For example, one trial enrolled 34 men with CRPC with progression after docetaxel and treated them with docetaxel 60 mg/m^2 and carboplatin area under the curve (AUC) 4 every 3 weeks.[47] The patients on the study were required to have experienced progression either during docetaxel therapy or shortly after its completion. Responses to the combination were observed, but the rates were low (objective response rate of 14%, >50% PSA response rate of 18%).

Carboplatin-paclitaxel has been similarly explored in docetaxel-refractory CRPC patients, on the basis that a different taxane may retain efficacy in the setting. In a Phase II trial of patients with progressive disease after docetaxel therapy, patients were treated with paclitaxel 135 mg/m^2 and carboplatin AUC three every 2 weeks.[48] Of 38 enrolled patients, 10 (26.3%) had a >50% PSA response and 10 an objective response in measurable lesions. This approach has not been tested in a randomized trial comparing it to other palliative second-line options.

The addition of platinum to docetaxel or paclitaxel may benefit selected patients with CRPC who are progressing on the taxane. However, whether patients would have greater benefit with the established second- and third-line agents is not known.

Platinum combinations for CRPC with small-cell features

One unusual aspect of adenocarcinomas of the prostate is that they pose a risk for developing a neuroendocrine or small-cell phenotype during treatment. While small-cell carcinoma can arise *de novo* in the prostate (as it can in essentially any extrapulmonary location), this feature of transformation from adenocarcinoma is somewhat unique in prostate cancer. Cases of small-cell transformation are characterized by unusual clinical characteristics including visceral metastases, high lactate dehydrogenase, lytic bone lesions, and lack of concordance between PSA changes and clinical progression.[49] Although small-cell transformation is infrequently diagnosed, autopsy studies on patients who died from CRPC suggest it may have occurred in up to 10% of cases.[50] Platinum-based combination chemotherapy is the treatment of choice for patients who have small-cell carcinoma is diagnosed. Prospective data are relatively lacking to guide treatment with chemotherapy, and patients are generally treated along a paradigm of extensive stage small-cell lung cancer.

Chemotherapy regimens employed for patients with CRPC transformed to small-cell carcinoma contain a platinum agent and either etoposide or docetaxel. Trials specifically in CRPC were broadly inclusive for patients with clinical features consistent with small-cell carcinoma, not specifically for those with a histologic diagnosis. In the GETUG P01 trial, for example, sixty patients with CRPC with features of neuroendocrine differentiation or visceral metastases were treated with carboplatin AUC 4 on day 1 and etoposide 100 mg/m^2 on days 1–3 of a 21-day regimen.[51] The authors reported overall survival of 9.6 months, consistent with the poor prognosis of the disease. Another trial employed sequential carboplatin AUC 5 plus docetaxel 75 mg/m^2 every 3 weeks, then after progression treatment with cisplatin 25 mg/m^2 plus etoposide 120 mg/m^2 for 3 days every 3 weeks.[52] Again, histologic confirmation of small-cell carcinoma was not required for admission to the study, but instead the eligibility criteria consisted of adverse features that were felt to be likely representing small-cell transformation. The patients treated on this study achieved a median overall survival of 16 months.

The overall prognosis remains poor for these patients, yet this entity is poorly studied. Improvement in outcomes with chemotherapy for patients with CPRC and small-cell transformation remains an area of significant need in the field.

BIOMARKERS ASSOCIATED WITH CHEMOTHERAPY EFFICACY

Through the study of the above agents, several clinical and laboratory characteristics have emerged as being associated with response and survival. While many of these markers are prognostic, the discovery of predictive biomarkers to guide therapy decisions remains under development. Biomarker identification is one of the most active areas of research currently in CRPC, and advances in this field will

eventually aid physicians to determine the best treatment options for patients.

PSA decline

A decline in PSA in response to therapy has been associated with improved overall survival in multiple studies of chemotherapy for CRPC. Both Phase III trials of docetaxel plus prednisone in metastatic CRPC have had an analysis of PSA responses with regard to overall survival. In the SWOG 9916 study, Petrylak *et al.* reported that a 30% decline in PSA at 3 months was associated with a 50% reduced risk of death.[53] Interestingly, a 30% PSA response – not a 50% response that typically has defined the threshold as a PSA responder – was most prognostic in this study. A similar analysis was performed among the patients treated in the TAX327 study.[54] A 30% PSA response at 3 months was confirmed as the best PSA surrogate endpoint for patients treated with docetaxel plus prednisone or mitoxantrone plus prednisone. A subsequent meta-analysis of 22 trials that incorporated docetaxel in the treatment for CRPC confirmed the association between the 30% PSA response and overall survival.[55]

PSA declines have also been examined for patients treated with cabazitaxel.[56] A PSA decline after 3 months of treatment with cabazitaxel was associated with reduced risk of death (HR = 0.52, $P < 0.001$). However, a PSA decline of 30% was not confirmed as a surrogate endpoint for overall survival. While PSA decline may be informative of prognosis, strategies of therapy changes based on this biomarker have not been validated.

Neutrophil-to-lymphocyte ratio

A high neutrophil-to-lymphocyte ratio (NLR) signals an inflammatory state in a patient and has prognostic value. Baseline NLRs have been investigated for prognostic characteristics in patients with CRPC treated with chemotherapy. In one such study, NLR was examined for prognostic value among patients treated in one of two Phase III studies of docetaxel plus prednisone for CRPC.[57] The investigators found that an NLR ≥2.0 at study entry was associated with poorer overall survival (HR = 1.29, $P < 0.001$). While prognostic, it was not predictive, and patients with both low and high NLR were shown to benefit from the therapy.

A similar retrospective analysis of cabazitaxel data confirmed the negative prognostic value of a high NLR.[58] In an analysis of the TROPIC trial, an NLR ratio of ≥3.0 was associated with risk of death (HR = 1.5, $P = 0.011$). In addition, a high NLR was also associated with a lower rate of PSA or objective response. Patients whose NLR changed from high to low during therapy had improved outcomes compared to those that remained high.

While a high NLR may be prognostic, it does not appear to be unique to any types of chemotherapy and is not likely to inform decision making with regard to therapy choice.

Circulating tumor cell enumeration

Circulating tumor cells (CTCs) can be counted in blood samples from patients with CRPC through a variety of methods, including the FDA-approved CellSearch technology by Veridex. The prognostic value of elevated CTC number was confirmed in a prospective trial in patients with CRPC starting treatment with chemotherapy. In this trial, 231 patients were evaluated with baseline and serial measurements of CTC counts.[59] An unfavorable CTC profile was defined as ≥5 CTCs in a 7.5 ml phlebotomy specimen. A favorable profile was defined as <5 CTCs. Baseline CTC characteristics were strongly correlated with overall survival. Those with unfavorable counts survived a median of 11.2 months less than those with favorable counts (11.5 vs. 22.7 months, HR = 3.3, $P < 0.001$). Conversion of a patient's CTC profile was associated with improved outcomes while the conversion from favorable to unfavorable was associated with poor outcomes. The FDA approved the CellSearch assay based on these data for prognostication in CRPC. Subsequently, CTC enumeration has been incorporated into prospective trials (e.g., Phase III trials of abiraterone[60]) although it has not yet been employed as a surrogate primary endpoint for registrational trials.

CTC data are not available from the TAX327 or TROPIC studies. Other prospective investigations of the prognostic value of CTC counts have been reported. One example of such a study is SWOG 0421, which was a Phase III study of docetaxel plus prednisone with or without atrasentan in patients with CRPC.[61] In this study, baseline and day 21 CTC counts were obtained. Patients with unfavorable CTCs at baseline had significantly worse overall survival compared to those with favorable profiles (13 vs. 26 months, HR = 2.7, $P < 0.001$). In addition, any rise in CTC counts on the second measurement was prognostic of poor survival. Whether outcomes would be affected by switching to alternate therapy early in such patients is unknown.

Androgen receptor splice variant 7

The AR can undergo alternative messenger RNA (mRNA) splicing resulting in several isoforms; the most clinically important of these splice variants is AR-V7. AR-V7 lacks the ligand-binding domain and functions as a constitutively active growth factor. Using an assay to analyze RNA isolated from CTCs, the expression of AR-V7 in CTCs was found to be associated with a lack of response to AR-directed therapy (viz., abiraterone or enzalutamide).[62] The expression of AR-V7 as a predictive biomarker was similarly investigated among patients being treated with chemotherapy.

In the first of these studies, 37 patients with CRPC starting treatment with either docetaxel ($n = 30$) or cabazitaxel ($n = 7$) were evaluated for the presence of detectable AR-V7 mRNA in CTCs.[63] Of these patients, 17 were positive for AR-V7. PSA responses (41% vs. 65%, $P = 0.19$), radiographic

progression-free survival (HR = 2.7, $P = 0.11$ in multivariate model), and overall survival (HR = 0.7, $P = 0.66$ in multivariate model) were all not significantly different between the AR-V7 positive patients and the AR-V7 negative patients. Authors concluded that while AR-V7 was associated with a poor response to AR-directed therapy, expression of AR-V7 in CTCs was not found to be similarly associated with a resistance to taxane chemotherapy.

Another group investigated the impact of AR-V7 on patients initiating cabazitaxel plus budesonide on a Phase II pharmacodynamic study.[64] Of the 29 patients who had samples tested, 16 were positive for CTCs with AR-V7 at the initiation of therapy. This study confirmed the results from the study of Antonarakis *et al.* There were no differences between AR-V7 positive and negative patients with regard to response rates (for reduction in CTCs or PSA), progression-free survival (HR = 0.8, $P = 0.6$), or overall survival (HR = 1.6, $P = 0.4$) observed.

While the detection of AR-V7 in CTCs of patients with CRPC may be predictive of primary resistance to AR-directed therapy, it does not appear to be associated with resistance to taxanes. Authors of these studies hypothesize that patients with AR-V7 positivity may be best served by treatment with chemotherapy instead of abiraterone or enzalutamide. However, the sample size in these studies is limited, and a prospective trial is needed.

CTC heterogeneity

A potential emerging biomarker is CTC heterogeneity. Scher *et al.* have presented data on the heterogeneity of CTCs and response to AR-directed therapy and chemotherapy.[60] In this study, individual CTCs were identified and isolated from patient blood samples. The individual cells were characterized based on a variety of different features including AR expression, size, and shape. Based on this characterization, patients were assigned as having either low or high heterogeneity. CTCs characterized as having high phenotypic heterogeneity were found to have higher genomic heterogeneity. High heterogeneity was associated with significantly shorter progression-free survival and overall survival for patients treated with AR-directed therapy. However, it was not associated with inferior outcomes for treatment with taxanes.

The author reported that the presence of a specific CTC subtype ("cell type K") was associated with decreased survival in the 71 patients who were started on taxane therapy (HR = 2.3, $P = 0.02$). Similar to the AR-V7 data, it is hypothesized that patients with high CTC heterogeneity may be most responsive to taxane chemotherapy and not AR-directed therapy. However, this data have been presented in abstract form only to this point, and confirmation and peer review of the data are needed.

CONCLUSIONS AND FUTURE CHALLENGES

As the treatment options for patients with metastatic CRPC continue to expand in coming years, defining the best time to treat patients with chemotherapy will be an important question to answer. The paradigm for docetaxel use is already shifting from late in the disease course to upfront at the diagnosis of metastatic disease. We do not know the optimal treatment strategy for patients who received docetaxel as per CHAARTED or STAMPEDE on the development of castration-resistant disease. The questions for these patients include whether they should be rechallenged with docetaxel or have cabazitaxel as "first-line" CRPC therapy. In addition, cross-resistance between novel hormonal agents is now recognized as a significant problem, and the use of chemotherapy instead of sequential AR-directed therapy may be the preferred strategy in the future. The identification and targeting of prostate cancer stem cells is an area of discovery being actively investigated.[65] While oncologists have several biomarkers to use to provide prognostic information to patients when treated with chemotherapy, the biggest future challenge will be in the development of predictive biomarkers to help choose the best therapies. CTC AR-V7 status and heterogeneity both appear to be excellent candidate biomarkers, and a prospective trial of AR-directed therapy versus chemotherapy therapy based on CTC biomarker status is needed to answer this question.

Financial support and sponsorship

This work was partially supported by the Conquer Cancer Foundation of ASCO Young Investigator Award (B.A.T.)

Conflicts of interest

There are no conflicts of interest.

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