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INVITED REVIEW

Prostate Cancer

Chemotherapy and its evolving role in the management of advanced prostate cancer

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Advanced prostate cancer has been recognized as being responsive to androgen deprivation since the 1940s when Charles Huggins first described the role of surgical castration in managing these patients. However, androgen deprivation only results in transient disease control for the vast majority of men, with those progressing in spite of castrate testosterone levels labeled as having castrate-resistant prostate cancer (CRPC). Until 2004, the therapeutic arena for these patients had remained stagnant, with no agent having shown a survival gain in the CRPC setting. Two landmark publications changed the prostate cancer treatment landscape by providing 'level-1 evidence' that docetaxel-based chemotherapy led to prolongation in overall survival (OS). This was followed by the approval of cabazitaxel in 2010 on the basis of Phase III data demonstrating its efficacy in patients pretreated with docetaxel. More recently, a number of next-generation androgen-directed agents (e.g. abiraterone and enzalutamide) have also been shown to lead to a survival benefit in men with CRPC. With so many new treatment options available, a number of questions remain. These include: how to best sequence chemotherapy with these newer hormonal agents, the clinical implication of cross-resistance between taxanes and androgen-directed agents and which subsets of patients may benefit most from early use of chemotherapy. This review will provide an overview of the evolving role of chemotherapy in the management of advanced prostate cancer in the current era.
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INTRODUCTION

Prostate cancer remains a major health concern, with an estimated 238 590 new cases and 29 720 deaths expected in the United States in 2013.[1] Since the 1940s, the initial management of advanced prostate cancer has entailed androgen ablation—either through surgical or medical castration (i.e. androgen deprivation therapy).[2] In spite of greater than 90% of men initially responding to androgen ablation, the disease will almost universally progress.[3] Upon progression despite androgen deprivation therapy, and in the presence of persistently suppressed serum testosterone levels (<50 ng dl^{-1}), patients are labeled as having castrate-resistant prostate cancer (CRPC).[4] Until 2004, the therapeutic arena had remained stagnant, with no agent having shown a survival gain in the CRPC setting. The landmark publications in 2004 by Petrylak and colleagues as well as Tannock and colleagues changed the prostate cancer treatment landscape by providing 'level-1 evidence' that docetaxel and prednisone, either with or without estramustine, lead to prolongation in overall survival (OS).[5,6]

More recently, the management of men with CRPC has made additional strides with the advent of newer androgen-directed therapies.[7] These agents have been developed in the context of realizing that tumors in men with CRPC are still largely dependent on AR signaling.[8] Indeed, a number of mechanisms have been elucidated by which androgen receptor (AR) signaling may continue to drive prostate cancer growth in spite of castrate serum testosterone levels. These included: (i) upregulation of the AR, (ii) increased extragonadal (adrenal, intratumoral and prostatic) testosterone synthesis via the cytochrome P450–17 (CYP-17) biosynthesis pathway, (iii) the emergence of constitutively activated AR splice variants, (iv) activation of androgen-AR signaling via alternative pathways and (v) AR coactivator expression.[9-15] Mechanistically, these newer androgen-directed agents work primarily through ligand depletion (e.g. abiraterone and orteronel) or through interference with AR trafficking and signaling (e.g. enzalutamide and ARN-509), with abiraterone and enzalutamide recently becoming approved for men with metastatic CRPC (mCRPC).[16-18]

With this explosion in the number of oral androgen-directed therapies either approved or expected to gain approval in coming years, the question remains as to what role chemotherapy will play in the management of patients with mCRPC and how it will fit into our contemporary treatment paradigm. Furthermore, evidence has begun to emerge that taxanes may partially function through inhibiting AR expression and trafficking into the nucleus of prostate cancer cells, leaving the possibility that the taxanes and newer androgen-directed therapies may have a significant degree of cross-resistance.[19,20] In this article, we will review the currently approved chemotherapeutics for the treatment of advanced prostate cancer with a focus on mechanisms of action, evidence of efficacy, mechanisms of resistance and potential interaction with some of the newer androgen-directed therapies.

EARLY EXPERIENCE WITH CHEMOTHERAPY IN PROSTATE CANCER

Mitoxantrone

The anthracenedione mitoxantrone was approved in 1996 for men with symptomatic mCRPC on the basis of data that it led to improvements

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in quality of life (QoL) and pain reduction.[21,22] A Phase III multicenter Canadian study randomized 161 men with mCRPC and bone pain to either prednisone or mitoxantrone plus prednisone.[21] A palliative response, defined as a 2-point decrease in pain assessed using a 6-point pain scale (or complete loss of pain if initially 1+), was the primary endpoint. The mitoxantrone-prednisone combination was found to lead to significantly more men achieving a palliative response (29% *vs* 12%; $P = 0.01$). However, the prostate-specific antigen (PSA) response rates (i.e. ≥50% PSA declines) between groups was not different (33% *vs* 22%, $P = 0.11$) and no difference in OS was observed either. A secondary analysis of QoL on that study was subsequently reported by Osoba and colleagues.[22] QoL was assessed using two surveys: the European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire C30 (EORTC QLQ-C30) and the Quality of Life Module-Prostate 14 (QOLM-P14). Overall, those in the mitoxantrone-prednisone groups were found to have significant improvements in global QoL compared to controls ($P = 0.009$). Given these encouraging palliative benefits and the lack of alternative therapeutic options at that time, mitoxantrone (given together with prednisone) was approved for men with mCRPC.

The aforementioned trial was not powered to detect differences in survival between those receiving mitoxantrone versus those that did not. A larger trial ($n = 242$) conducted by the Cancer and Leukemia Group B (CALGB), the CALGB 9182 study, was developed in an attempt to determine if mitoxantrone produced improvements in OS.[23] While PSA responses (i.e. ≥50% PSA decline) were more common (38% *vs* 22%, $P = 0.008$) and there was a significant delay in progression-free survival (PFS) with the combination of mitoxantrone plus hydrocortisone compared to hydrocortisone alone (median PFS 3.7 *vs* 2.3 months, $P = 0.022$), no difference in OS between the groups was observed (median OS 12.7 *vs* 12.3 months, $P > 0.05$). Furthermore, when the mitoxantrone group was compared to the placebo group there were no differences in objective radiographic responses (i.e. complete response plus partial response rate; 7% *vs* 4%, $P = 0.375$) or in global QoL as assessed using the Functional Living Index-Cancer (FLIC). There were differences between the two groups in the emotional state subscale, family disruption subscale and two pain items. The lack of clear objective benefits reported in these two trials illustrated the profound need for more effective treatment options during this time period.

At the current time, despite the lack of survival benefit with mitoxantrone, this chemotherapy may still have a role in the second-line (post-docetaxel) setting in particular patients. Although the novel taxane agent cabazitaxel is superior to mitoxantrone in this setting (see TROPIC trial, below), mitoxantrone is associated with lower rates of myelosuppression and may be a reasonable chemotherapy option in a patient with poor bone marrow reserves or performance status 2–3. Because of its palliative effects, mitoxantrone may be especially useful in docetaxel-pretreated patients with symptomatic bone pain who may not tolerate cabazitaxel.

Cyclophosphamide

Another chemotherapeutic option commonly utilized in the pre-docetaxel era to treat men with mCRPC was oral cyclophosphamide. A handful of investigators have reported response rates in the range of 20%–40% when given as monotherapy or in combination with other agents (both PSA and objective response criteria).[24-30] In one of the early studies, Raghavan and colleagues administered cyclophosphamide at 100 mg daily by mouth on days 1–14 of a 28-day cycle. Thirty patients were treated in total, and they reported a median OS of 12.7 months from the date of cyclophosphamide initiation, partial responses (per the National Prostatic Cancer Project criteria) in six (20%) subjects and disease stabilization in 13 (43%) subjects.[24] In addition, 18 (60%) patients experienced a major reduction in tumor-associated symptoms and 21 (70%) had significant pain reductions. Another report by Nicolini and colleagues ($n = 8$) evaluated continuously-dosed oral cyclophosphamide at a dose of 100–150 mg daily.[26] They reported two partial responses and three patients with stable disease while the other three subjects progressed (per Prostate-Specific Antigen Working Group criteria). In those who responded to treatment ($n = 5$), the median OS from the time of cyclophosphamide commencement was 17 months and duration of clinical benefit was reported at 9 months. In addition, a number of trials have evaluated cyclophosphamide in combination with other chemotherapeutics (e.g. etoposide, estramustine and tegafur), and while response rates may appear to be slightly improved compared to monotherapy, to the best of our knowledge there have been no trials directly comparing cyclophosphamide combination therapy to monotherapy.[27-29]

MICROTUBULE-MODULATING AGENTS

Microtubules are dynamic filamentous proteins that are implicated in a range of cellular functions including: providing integrity and preserving cellular architecture, mitosis, cellular protein transport, cell signaling and gene expression.[31,32] Microtubules are composed of polymerized tubulin, which exists as a heterodimer of alpha- and beta-tubulin subunits. A guanosine triphosphate (GTP)-fueled equilibrium between the free and polymerized tubulin subunits is responsible for a state referred to as 'dynamic equilibrium', leading to the plasticity exhibited by microtubules and their resultant broad range of functions. Given the host of vital cellular functions that microtubules are involved in, a number of antineoplastic agents have been developed to act as microtubule inhibitors. To date, the most efficacious chemotherapeutic agents in prostate cancer all function as microtubule inhibitors (i.e. docetaxel, cabazitaxel and estramustine).

Interestingly, while 'chemotherapy' is traditionally not considered targeted therapy, a number of preclinical experiments have implicated microtubules in androgen-AR signaling. Given the well-described link between AR signaling and prostate cancer proliferation, this potentially provides a mechanistic insight into why agents like docetaxel are effective prostate cancer therapies; whereas, other chemotherapeutics have produced only marginal response rates.[31] It has recently emerged that taxanes are able to modulate AR-mediated transcription, as evidenced by their ability to decrease expression of the androgen-mediated genes *PSA* and *NKX3.1*, while increasing expression of maspin (an androgen-repressed gene).[33] It has also been shown that taxane-based therapies are able to inhibit AR nuclear localization through the disruption of normal microtubule function.[19] Human prostate tissue microarrays from subjects who were pre- and post-docetaxel treatment have also demonstrated decreased AR nuclear localization following treatment with docetaxel (50% nuclear localization in chemotherapy-naïve specimens compared to 38% in docetaxel-pretreated specimens).[19] Furthermore, a small pilot study evaluating the effect of taxanes on AR localization in circulating tumor cells from patients confirmed this finding. In that study, taxane-responders were defined as having a ≥30% decline in PSA, progressors as having > 25% PSA increase and stable disease fulfilling neither of these criteria. The investigators found that 12/17 patients (70.6%) with response or stable disease had cytoplasmic AR localization, while 13/18 (72%) of progressors had nuclear AR localization ($P = 0.02$).[34]

Estramustine

Estramsutine was initially approved for men with CRPC in 1984. It is a nitrogen mustard-estradiol conjugate that was originally designed for the treatment of estrogen receptor (ER)-positive cells; however, significant ER binding is not observed nor does it display clinical effects consistent with other alkylating agents (e.g. neutropenia).[31] It is a somewhat unique agent in that it has been shown to exert both hormonal and non-hormonal effects.[35] The metabolic products of estramustine phosphate (the parent compound) include estrone and estradiol. These two metabolites have been shown to exert anti-gonadotrophic properties leading to decreases in serum testosterone.[36] Estramustine, the key cytotoxic metabolite, on the other hand has been shown to cause microtubule depolymerization through a direct tubulin interaction.[37] Additionally, *in vitro* data demonstrate a strong degree of synergy between estramustine and a number of other chemotherapeutic agents.[38]

Early monotherapy trials revealed only modest anti-prostate cancer effects. As part of the National Prostatic Cancer Project (NPCP), six randomized trials evaluated estramustine as monotherapy. Only 5% of 304 total enrolled patients had objective responses.[39,40] Other studies of single-agent estramustine have demonstrated objective response rates in the range of 20%–50%.[31] While only modestly effective as a single-agent, based on the aforementioned preclinical work, it was hypothesized that estramustine may exhibit synergy with other microtubule-inhibiting and cytotoxic agents. As such, a number of combination studies were conducted in the 1990s to mid-2000s—the most well-known of which was the Phase III Southwest Oncology Group (SWOG) 9916 study that demonstrated a survival advantage with the combination of estramustine and docetaxel compared to mitoxantrone.[5,41,42]

Docetaxel

Docetaxel is a semisynthetic taxane, which functions as a microtubule inhibitor through binding to beta-tubulin and preventing microtubule disassembly. This inability to disassemble effectively 'locks' microtubules in a polymerized state, halting dynamic equilibrium and resulting in the disruption of key microtubule functions such as mitosis (typically at the G_2/M phase) and AR nuclear translocation.[19,34,43] In addition, there is evidence that docetaxel is capable of inhibiting expression of *BCL-2* and *BCL-X*, two anti-apoptotic genes, thereby promoting apoptosis **(Table 1)**.[43,44]

A number of early-phase trials evaluating the utility of single-agent and combination therapy with docetaxel plus estramustine have been completed. Typically, these studies have evaluated either weekly or every-3-week dosing schedules, with 30 and 75 mg m^{-2} being the most frequently employed doses, respectively. Both schedules have demonstrated efficacy in the Phase II setting. For instance, two trials evaluating a 21-day dosing schedule reported partial objective response rates of 17%–28% and PSA declines ≥50% in 38–46% of patients.[45,46] Similarly, a Phase II study testing a weekly schedule of docetaxel (6 weeks on, 2 weeks off) demonstrated ≥50% PSA declines in 41% of patients and a median OS of 9.4 months.[47]

Based on these encouraging early-phase data, docetaxel was moved to Phase III testing and was approved in the mCRPC setting on the basis of two landmark Phase III trials: the TAX-327 study and the SWOG-9916 study.[5,6] The first trial by Tannock and colleagues (TAX-327) randomized patients to prednisone (5 mg twice daily) plus one of three chemotherapy regimens: docetaxel 75 mg m^{-2} on day 1 of a 21-day cycle (n = 335), docetaxel 30 mg m^{-2} weekly for the first 5 weeks of a 6 week cycle (n = 334) or mitoxantrone 12 mg m^{-2} on day 1 of a 21-day cycle (n = 337). The median OS observed in the 21-day schedule of docetaxel, weekly schedule of docetaxel and mitoxantrone groups were 18.9, 17.4 and 16.5 months, respectively. Only the 21-day schedule was found to lead to a statistically significant increase in OS compared to the mitoxantrone arm (hazard ratio [HR], 0.76; 95% confidence interval [CI], 0.62–0.94; P = 0.009), while the HR for survival fell just short of significant for the weekly docetaxel dosing schedule (HR, 0.91; 95% CI, 0.75–1.11; P = 0.36). The response rate for the 21-day schedule of docetaxel was 35% compared to 22% for mitoxantrone (P = 0.01). Updated survival data from TAX-327 demonstrated that the survival advantage seen with 21-day docetaxel has persisted, and in fact the median OS with longer follow-up increased to 19.2 months compared to 16.3 months with mitoxantrone (P = 0.004) (still without a significant improvement with weekly docetaxel).[48] In addition, there were significant improvements in pain and QoL scores for those receiving the 21-day schedule of docetaxel. A subsequent *post hoc* analysis revealed that those with significant pain at enrollment were most likely to experience improvements in QoL (92% *vs* 75%, P < 0.001), speaking to the palliative benefits of this regimen in those with more symptomatic disease.[49] Most types of adverse events were more common with docetaxel compared to mitoxantrone. There was notably no difference in the frequency of adverse events with weekly docetaxel compared with the 21-day docetaxel schedule. Grade ≥3 toxicities seen with docetaxel included anemia (5%), thrombocytopenia (1%) and neutropenia (32%). Other adverse events of interest include: diarrhea (32%), sensory neuropathy (30%), stomatitis (20%) and peripheral edema (19%).

The second Phase III trial testing docetaxel in men with mCRPC (SWOG-9916) was published by Petrylak and colleagues.[5] In that report, docetaxel was combined with estramustine, an agent that had demonstrated modest single-agent activity, but displayed evidence of synergy with other microtubule-inhibiting agents in both the preclinical and clinical setting.[38,41] In that trial, men were randomized to one of two regimens (both administered on a 21-day schedule): estramustine 280 mg three time daily on days 1–5, docetaxel

Table 1: Postulated mechanisms of action and resistance for docetaxel

	References
Mechanisms of taxane action	
Microtubule inhibition, resulting in disruption of mitosis	Pienta 2001[43]
Inhibition of the expression of the anti-apoptotic genes *BCL-2* and *BCL-X*	Haldar *et al.*, 1997[75]
Inhibition of microtubule-mediated androgen receptor (AR) nuclear transport	Gan *et al.*, 2009[33] Zhu *et al.*, 2010[19] Darshan *et al.*, 2011[34]
Mechanisms of taxane resistance	
Intrinsic to prostate cancer biology	
AR upregulation	Kokontis *et al.*, 1998[10]
Increased extragonadal androgen synthesis	Stanbrough *et al.*, 2006[11] Montgomery *et al.*, 2008[12]
Emergence of constitutively active AR splice variants	Nacusi, 2009[13]
Activation of alternative androgen-AR signaling pathways	Weber and Gioeli, 2004[14]
AR coactivator expression	Gregory *et al.*, 2001[15]
General resistance mechanisms	
Limited tumor/tissue penetration	Kyle *et al.*, 2007[76]
Inherently resistant subpopulation of cells	Maitland and Collins, 2008[77]
Multidrug resistance efflux pump	Kawai *et al.*, 2000[53] Oprea-Lager *et al.*, 2013[54]

60 mg m^{-2} on day 2 and dexamethasone 60 mg in three divided doses prior to docetaxel (n = 338) versus mitoxantrone 12 mg m^{-2} on day 1 plus prednisone 5 mg twice daily (n = 336). Again, docetaxel was shown to lead to a statistically significant improvement in OS compared to mitoxantrone in this trial, with the median OS reported at 17.5 and 15.6 months, respectively (P = 0.02). PSA declines ≥50% were observed in 50% of patients treated in the docetaxel arm compared to 27% of those in the mitoxantrone arm (P < 0.001). There was no significant difference in objective tumor responses between the two arms. Unlike TAX-327, SWOG-9916 failed to show any differences in pain control between the two groups.

While direct comparison between these two Phase III studies is fraught with problems, the results from the TAX-327 trial perhaps imply slightly better outcomes compared to the SWOG-9916 study. A Phase II trial randomizing 150 patients between docetaxel either with or without estramustine found that, while PSA response rates were not statistically different, toxicities were increased with the addition of estramustine to docetaxel. In total, grade 3/4 toxicities occurred in 45% compared to 21% (P = 0.005) in the docetaxel-estramustine and docetaxel groups, respectively.[50] In addition, the use of estramustine has been associated with venous thromboembolic events. The current National Comprehensive Cancer Network (NCCN) guidelines reflect these observations and recommend against the addition of estramustine to docetaxel in the treatment of mCRPC.[51]

Cabazitaxel

One of the proposed mechanisms by which docetaxel resistance may emerge is through the P-glycoprotein-associated multidrug resistance efflux pump. [52–55] Cabazitaxel is a next-generation taxane, which like docetaxel, functions through binding beta-tubulin and preventing depolymerization of microtubules.[31] While it displays similar anticancer efficacy to docetaxel in taxane-sensitive *in vitro* models, it has been shown to have enhanced efficacy in cell lines with P-glycoprotein overexpression.[56] This data formed the basis for testing cabazitaxel in the post-docetaxel setting in men with mCRPC.

The seminal Phase III TROPIC trial assessed prednisone 10 mg daily plus cabazitaxel 25 mg m^{-2} (n = 378) versus mitoxantrone 12 mg m^{-2} (n = 377) in men with mCRPC who had progressed during or after treatment with docetaxel.[57] The median survival with cabazitaxel in this trial was 15.1 months compared to 12.7 months with mitoxantrone (HR, 0.70; 95% CI, 0.59–0.83; P < 0·0001). There was no improvement in pain with cabazitaxel compared to mitoxantrone. Radiographic (14.4% *vs* 4.4%, P = 0.0005) and ≥50% PSA response rates (39.2% *vs* 17.8%, P = 0.0002) were observed at a higher frequency with cabazitaxel compared to mitoxantrone. Grade ≥3 adverse events that were more frequently seen with cabazitaxel included neutropenia (82%) and diarrhea (6%). Interestingly, unlike docetaxel, peripheral neuropathy was rare, with grade-3 neuropathy occurring in < 1% of patients and all-grade neuropathy in 14% of patients treated with cabazitaxel. While not statistically different, there were more treatment-related deaths (i.e. within 30 days of last infusion) observed in the cabazitaxel arm (5% *vs* 2%), raising potential questions about cabazitaxel's safety especially in elderly populations. It should be noted, however, that the TROPIC trial precluded the use of granulocyte colony-stimulating factor as primary prophylaxis. Based on the aforementioned safety concerns, it is now recommended by the American Society of Clinical Oncology guidelines as well as the cabazitaxel prescribing information brochure to consider granulocyte colony-stimulating factor prophylaxis in high-risk patients (e.g. age > 65 years, poor performance status, prior episodes of febrile neutropenia, extensive prior radiation ports, poor nutritional status or other serious comorbidities). Ultimately, based on the favorable overall results of the TROPIC trial, the Food and Drug Administration approved cabazitaxel in 2010 for the second-line treatment of patients with mCRPC who had previously received docetaxel. This approval has, in turn, resulted in a diminished use of mitoxantrone (although the latter may still be a reasonable option in men who may not tolerate cabazitaxel).

It should be noted that both cabazitaxel 20 and 25 mg m^{-2} every 21 days were recommended for Phase II/III testing based on early-phase trials.[56,58,59] Whether or not 20 mg m^{-2} of cabazitaxel may be equally efficacious compared to the 25 mg m^{-2} dose tested in the TROPIC trial is not known. According to the TROPIC investigators, the decision to proceed with 25 mg m^{-2} was made given the desire to assess 'as effective a dose as possible' as well as data from a Phase II trial in breast cancer patients showing that an increase in dose from 20 to 25 mg m^{-2} was not associated with increased toxicity.[60] Needless to say, it remains unclear if a lower dose of cabazitaxel (i.e. 20 mg m^{-2}) would have an improved therapeutic ratio with equipotent antitumor efficacy. The PROSELICA trial, a Phase III noninferiority trial with an OS primary endpoint, was launched in order to answer this question by randomizing docetaxel-pretreated patients between these two dose levels (clinicaltrials.gov, NCT01308580).

Another question that remains unanswered is whether cabazitaxel is effective pre-docetaxel (i.e. in the first-line setting). Several trials have been launched in an effort to address this issue. The phase III FIRSTANA trial randomizes patients between three arms: cabazitaxel 20 mg m^{-2}, cabazitaxel 25 mg m^{-2} or docetaxel 75 mg m^{-2} (clinicaltrials.gov, NCT01308567). All are given in conjunction with prednisone and are dosed on a 21-day schedule. Enrollment to this trial was recently completed, and patients will now be followed for survival. Another study which evaluates first-line cabazitaxel is the phase II TAXYNERGY trial (clinicaltrials.gov, NCT01718353).[61] In that trial, chemotherapy-untreated mCRPC subjects are randomized 2: 1 to either docetaxel 75 mg m^{-2} every 3 weeks (potentially followed by cabazitaxel) versus cabazitaxel 25 mg m^{-2} every 3 weeks (potentially followed by docetaxel), with a therapy switch occurring in patients who fail to achieve a PSA decline of ≥30% after four cycles of first-line taxane therapy (patients who do achieve a ≥30% PSA reduction in the first four cycles remain on the same taxane agent). The primary endpoint of TAXYNERGY is the PSA response rate (i.e. ≥50% PSA decline) during the whole treatment period, while PFS and OS are important secondary endpoints. In addition, this trial is evaluating microtubule engagement and trafficking of the AR using circulating tumor cells collected at baseline and at various follow-up time points, in an effort to understand mechanisms of response and resistance to both taxane agents.[62] These two trials will provide valuable information regarding the optimal sequencing of these two chemotherapeutics and the role of cabazitaxel in treating docetaxel-naïve patients.

COMBINATION TRIALS

The collective experience from a host of other malignancies has provided the impetus to evaluate combination therapeutic regimens as a means to improve response rates compared to single-agent chemotherapy. Unfortunately, to date, no combination regimen has proven to afford a survival advantage compared to single-agent taxane therapy alone. Docetaxel in combination with atrasentan, lenalidomide, aflibercept, bevacizumab and dasatinib (amongst other agents) have all proven to not be superior to single-agent docetaxel with respect to OS.[63-67] While there are several potential explanations for the failure of

eight consecutive phase III 'docetaxel-plus' studies, perhaps the most concerning observation was the lack of positive well-designed phase II trials before embarking on phase III testing.[68] A similar large number of trials evaluating cabazitaxel in various combinations are currently underway (**Table 2**).[55]

One potential strategy explored in earlier Phase trials is combing chemotherapy with an AR-targeted agent such as ketoconazole, abiraterone or enzalutamide. A Phase I study conducted at the National Cancer Institutes evaluated ketoconazole combined with weekly docetaxel.[69] This study reported PSA responses (≥50% PSA declines) in 62% of enrolled subjects. Furthermore, radiographic partial responses occurred in seven (28%) of 25 patients with soft tissue disease. A recently reported Phase I trial has shown that enzalutamide plus docetaxel is well-tolerated, and that docetaxel pharmacokinetics were not augmented by the coadministration of enzalutamide.[70] An additional Phase I study evaluating abiraterone in combination with docetaxel is ongoing (clinicaltrials.gov, NCT01400555). Whether this strategy of combining next generation androgen-directed agents and taxane-based chemotherapy will prove more effective than either single agent alone remains to be seen.

Currently, the only Phase III docetaxel-based combination trial with results still pending is a study of docetaxel with or without custirsen (previously called OGX-011). Custirsen is an antisense oligonucleotide inhibitor of the cytoprotective chaperone gene clusterin that has shown promise in two randomized Phase II trials.[71,72] Chi and colleagues reported that in chemotherapy-naïve patients randomized to docetaxel and prednisone with or without custirsen, there was a significant improvement in OS (a secondary endpoint) with the addition of custirsen when other relevant covariables were controlled for (HR 0.50, 95% CI: 0.29–0.87).[71] Saad and colleagues tested custirsen in patients progressing on docetaxel.[72] In that trial, subjects received prednisone and were randomized to also receive mitoxantrone plus custirsen or docetaxel retreatment plus custirsen. The docetaxel and mitoxantrone arms achieved a median OS of 15.8 and 11.5 months, respectively. Based on these results, two Phase III trials were launched. The SYNERGY trial is investigating custirsen in chemotherapy-naïve patients (clinicaltrials.gov, NCT01188187). In that trial, subjects are being randomized to docetaxel-prednisone with or without custirsen. The second Phase III trial, called AFFINITY, is evaluating custirsen in patients who have progressed on docetaxel (clinicaltrials.gov, NCT01578655). Patients on this study will receive cabazitaxel-prednisone with or without custirsen. Both trials have chosen OS as their primary endpoint.

CONCLUSIONS

In this era of next-generation androgen-directed therapies (e.g. abiraterone and enzalutamide) the role of cytotoxic chemotherapy is becoming less clear although still has a distinct role. While docetaxel, and to a lesser extent cabazitaxel, remain important treatment options for patients with advanced mCRPC, the efficacy of these newer AR-targeting agents makes these chemotherapies less desirable options for some patients. How to best incorporate cytotoxics into our current treatment paradigms is an issue that needs to be clarified. One strategy would be to reserve cytotoxics for patients with bulky visceral disease, rapidly expanding disease or those requiring rapid palliation. While comparative data between the androgen-directed therapies and chemotherapy are lacking, the fact that docetaxel has been reported to achieve a pain response after only 27 days and a QoL response after 43 days speaks to the rapidity with which chemotherapy is able to exert an antitumor effect.[40]

As discussed previously, an important consideration when using taxanes is the possibility of cross-resistance with agents that acts to inhibit signaling along the AR pathway (i.e. androgen-directed therapies). In the case of ketoconazole, a less potent CYP17 inhibitor than abiraterone, trends towards shortened PFS and OS with docetaxel therapy have been observed for those pretreated with ketoconazole compared to those that were not.[73] However, clinical outcomes with docetaxel-based chemotherapy (with or without bevacizumab) did not appear inferior in ketoconazole-pretreated patients in a *post hoc* analysis of the phase III CALGB-90401 trial.[74] Conversely, a small (n = 35) single-arm retrospective analysis of docetaxel outcomes in abiraterone-pretreated patients suggested inferior outcomes in this group compared to historical abiraterone-naïve patients.[75] For instance, median OS was reported at 12.5 months (95% CI, 10.6–19.4 months), which was considerably lower than the 19.2 months (95% CI, 17.5–21.3 months) observed on the TAX-327 study.[40] Suffice it to say, the optimal sequence of docetaxel with the newer androgen-directed therapies has yet to be established and is an area of active investigation.

If the trend over the last few years persists, androgen-directed therapies will continue to prove efficacious at earlier stages of CRPC, with chemotherapy continuing to move more distally in the treatment paradigm. Currently, key questions that remain unanswered include:

Table 2: Ongoing cabazitaxel-based combination trials

Clinicaltrials.gov identifier	*Phase*	*Patient population*	*Estimated enrollment*	*Treatment*	*Primary endpoint*
NCT01420250	I	Locally-advanced disease with unfavorable risk factors	30	Cabazitaxel plus radiation therapy	MTD of cabazitaxel
NCT01578655	III	Metastatic CRPC, post-docetaxel	630	Cabazitaxel plus custirsen *vs* Cabazitaxel alone	Overall survival
NCT01469338	II	Metastatic CRPC, post-docetaxel	50	Cabazitaxel plus octreotide	Development of grade-2 diarrhea (CTCAE v4.0)
NCT01594918	I	Metastatic CRPC, chemotherapy-naïve	42	Cabazitaxel plus mitoxantrone	MTD of combination
NCT01650285	II	Post-radical prostatectomy	24	Cabazitaxel plus radiation therapy	MTD of cabazitaxel
NCT01845792	I/II	Metastatic CRPC, post-docetaxel	72	Cabazitaxel plus abiraterone	Phase I: MTD of combination Phase II: PSA response
NCT01505868	I/II	Metastatic CRPC, post-docetaxel	178	Cabazitaxel plus carboplatin *vs* cabazitaxel alone	Progression-free survival
NCT01513733	I	Metastatic CRPC, post-docetaxel	32	Cabazitaxel plus tasquinimod	MTD of combination
NCT01511536	I/II	Metastatic CRPC, post-docetaxel	38	Cabazitaxel plus abiraterone	MTD of combination, PSA response

CRPC: Castrate-resistant prostate cancer; CTCAE: Common terminology criteria for adverse events; MTD: Maximum tolerated dose; PSA: Prostate-specific antigen

how to best sequence chemotherapy with these newer hormonal agents, the clinical implication of cross-resistance between taxanes and androgen-directed agents and which subsets of patients will benefit most from early use of chemotherapy. For the time being, chemotherapy (and docetaxel in particular) remains an important option for some men with prostate cancer; however, the future role of chemotherapies in managing our patients with advanced CRPC remains to be determined.

COMPETING INTEREST

None of the authors declare any financial or other potential conflicts of interest related to this work.

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