Chemotherapy in the Treatment of Prostate Cancer – The Past, the Present, and the Future

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Abstract

Chemotherapy is an important treatment modality in metastatic castration-resistant prostate cancer. Extensive clinical research for more than 3 decades has shown only a handful of chemotherapeutic agents to be active in metastatic prostate cancer. In this article, we aim to review the role of chemotherapy in the treatment of prostate cancer, focusing on historical studies, landmark trials, and the latest advancements.

Key Words: Prostate cancer, castratation-resistant, docetaxel.

Introduction

Prostate cancer is the most common nondermatologic malignancy in men. Routine screening, early diagnosis, newer treatment options, and the possibility of cure have increased prostate cancer survivorship impressively. In the United States it is estimated that 43% of male cancer survivors are prostate cancer survivors, and their 5-year survival across all stages is 99.7%.[1]

This increase in survivorship also necessitates that the medical community be mindful of morbidity associated with different treatment modalities. Treatment options for prostate cancer include surgery, radiation therapy, hormonal therapy, and chemotherapy. In this review, we will focus on the role, timing, benefits, and potential adverse effects (AEs) of chemotherapy in prostate cancer (which is commonly considered the most morbid of the treatment options, as well as the option most feared by patients).

Historical Perspective

Androgens have a pivotal role in the pathogenesis of prostate cancer, and androgen-deprivation therapy (ADT) has been the backbone for the treatment of locally advanced or metastatic prostate cancer since the 1940s. However, after 15 to 24 months, the majority of patients receiving ADT experience a rise in prostate-specific antigen (PSA), signifying resistance to ADT.[2-5] This rise is usually clinically silent, but it has led to the Prostate Cancer Working Group 2 (PCWG2) definition of metastatic castration-resistant prostate cancer (mCRPC).[6] That definition in turn has spawned a flood of research on the role of chemotherapy and other new agents in mCRPC (**Figure 1**). While most of the research on prostate cancer has focused on novel nonchemotherapeutic agents, several cytotoxic drugs have been used in mCRPC for many years. Moreover, newer cytotoxic agents are being studied in mCRPC with the goal of achieving FDA approval.[7]

During the 1990s, a number of studies concluded that chemotherapy had a minimal role in mCRPC because the agents tested at that time rarely showed palliation of symptoms or a survival advantage.[8-13] One of the problems with most of those early trials was that they were significantly underpowered to detect meaningful changes in survival, palliation, or even objective response. In addition, PSA had not yet been developed to guide therapeutic agent development.

Mitoxantrone

Although 5-fluorouracil and cyclophosphamide were able to palliate some patients with mCRPC in the early trials, mitoxantrone, a topoisomerase-2 inhibitor, was the first chemotherapy drug approved by the FDA for mCRPC. In a trial conducted in Canada, 161 patients with symptomatic mCRPC were randomized to receive either mitoxantrone plus prednisone or prednisone alone.[13] The main outcome measure was palliation of symptoms (ie, decrease in pain and need for analgesic medications). Palliative response was observed in 29% of patients who received mitoxantrone plus prednisone compared with 12% who received prednisone alone ($P = .01$).

A subsequent phase 3 trial was conducted in the United States with mitoxantrone in hormone-refractory prostate cancer. In this trial, mitoxantrone plus low-dose hydrocortisone was compared with hydrocortisone alone in 242 patients with symptomatic hormone-refractory prostate cancer. There was a statistically significant improvement in palliation of pain, but no difference in overall survival (OS).[14] These 2 studies led the FDA to approve mitoxantrone for mCRPC in 1999. A third phase 3 study comparing mitoxantrone plus prednisone versus prednisone alone in asymptomatic hormone-refractory prostate cancer showed objective decreases in PSA and increase in time to progression in the mitoxantrone arm, with no difference in OS.[15] Availability of newer drugs with better efficacy has limited the use of mitoxantrone in treatment of mCRPC to a third- or fourth-line drug for patients who are not candidates for other agents, such as radium 223 or cabazitaxel.[16]

Docetaxel

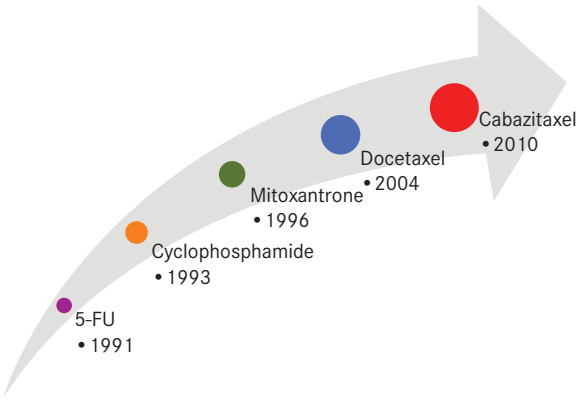
Taxanes are antimitotic agents that act by binding to tubulin and inhibiting disassembly of microtubules.[16] Paclitaxel, the pro-

totypic taxane, was initially thought to be inactive in mCRPC,[17] but Kreis et al[18] suggested strong activity of the newer taxane docetaxel in a series of cell line models. Subsequent phase 1 and 2 studies confirmed the activity of docetaxel in prostate cancer.[19] These data set the stage for 2 large phase 3 trials of docetaxel compared with mitoxantrone (both with a crossover design) in mCRPC.[20,21]

In the landmark TAX 327 phase 3 trial conducted March 2000 to June 2002, 1006 patients with mCRPC were randomized to receive daily prednisone and mitoxantrone 12 mg/m^2 every 3 weeks, or docetaxel 75 mg/m^2 every 3 weeks, or docetaxel 30 mg/m^2 weekly for 5 of every 6 weeks.[20] Patients who received docetaxel 75 mg/m^2 every 3 weeks had a median survival of 19.2 months compared with 16.3 and 17.8 months in the mitoxantrone and weekly docetaxel arms, respectively.[22] The arm that received docetaxel every 3 weeks yielded a hazard ratio (HR) for death of 0.76 (95% confidence interval [CI], 0.62-0.94; P = .009); the weekly docetaxel arm had a HR for death of 0.91 (95% CI, 0.75-1.11; P = .36). Docetaxel became the first chemotherapy agent that showed an OS benefit in mCRPC, and was approved for this indication in combination with prednisone by the FDA in 2004.

Petrylak et al[21] compared docetaxel in combination with estramustine to mitoxantrone and prednisone in a phase 3 trial. The docetaxel-plus-estramustine arm had a statistically significant OS advantage of nearly 2 months over the mitoxantrone arm (17.5 months vs 15.6 months; P = .02). In addition, time to progression was significantly longer in the docetaxel-plus-estramustine arm, and more patients had 50% PSA decline.

FIGURE 1. Evolution of Chemotherapeutic Agents in the Treatment of Metastatic CRPC



5-FU indicates 5-fluorouracil; CRPC, castration-resistant prostate cancer.

Docetaxel Combinations

Subsequently, multiple phase 3 trials have attempted to improve upon docetaxel's efficacy by combining it with other agents such as immune modulators, vascular endothelial growth factor receptor inhibitors, monoclonal antibodies, and tyrosine kinase inhibitors in the first-line setting. However, none of them showed an OS benefit compared with standard therapy with docetaxel and prednisone.[23-26]

Two of the largest negative trials are described here. In the CALGB 90401 trial, 1050 chemotherapy-naïve patients were randomized to receive standard docetaxel 75 mg/m^2 and prednisone with or without bevacizumab 15 mg/kg every 3 weeks.[24] The study arm with bevacizumab showed a significant progression-free survival (PFS) advantage (9.9 vs 7.5 months, stratified log-rank P <.001), but failed to show a statistically significant OS advantage (22.6 months in the bevacizumab arm compared with 21.5 months for patients treated with standard therapy [HR = 0.91; 95% CI, 0.78-1.05; stratified log-rank P = .181]). In addition, the bevacizumab arm had more treatment-related grade 3 and grade 4 neutropenia, fatigue, and hypertension compared with the control arm.

In the phase 3 MAINSAIL trial, 1059 chemotherapy-naïve patients with mCRPC were randomized to receive either lenalidomide 25 mg/day on days 1–14 in addition to standard docetaxel 75 mg/m^2 plus prednisone, or placebo on days 1–14 in addition to standard docetaxel 75 mg/m^2 plus prednisone every 3 weeks.[27] The study-defined primary end point was OS, and secondary end points were PFS, objective response rate, and safety. The median number of cycles administered were 6 and 8 in the lenalidomide and placebo arms, respectively.

The median OS and PFS were 77 weeks and 45 weeks in the lenalidomide-plus-docetaxel arm compared with median not reached (P = .0017) and 46 weeks (P = .0187) in the placebo-plus-docetaxel arm with a HR (lenalidomide vs placebo) of 1.53 (95% CI, 1.17-2.00) for OS and 1.32 (95% CI, 1.05-1.66) for PFS. Neutropenia-related complications were the most common AE in the lenalidomide arm, while grade 3 vascular events were reported in 7.2% versus 4.4 % in the lenalidomide and placebo arms, respectively. This study showed that adding lenalidomide to docetaxel did not improve OS and resulted in greater toxicity.[27]

Docetaxel Failure

When it became clear that docetaxel was the standard of care in CRPC,[28] multiple, small phase 2 studies looked at second-line drugs individually and in combination after docetaxel failure. Regimens such as cisplatin and prednisone, oxaliplatin and pemetrexed, oxaliplatin and capecitabine, and carboplatin and docetaxel showed activity in prostate cancer measured as decline in PSA, partial radiologic response in a setting of standard docetaxel therapy failure.[29-33] However, no phase 3 studies were done with these older agents to establish their role in the treatment of docetaxel-refractory prostate cancer. An exception to that rule was the study

TABLE. Major Chemotherapy Trials in Prostate Cancer Treatment

Study/Author	Year	Study Design	End Points/Results	Significant Toxicities in Study Arm
Tannock et al[13]	1996	Mitoxantrone + prednisone vs Prednisone (in patients with metastatic CRPC)	Palliative response (pain control) observed in 29% of mitoxantrone group compared with 12% in prednisone group	**Neutropenia** Grade 3: 32% Grade 4: 13%
Tannock et al[20,26]	2004	Docetaxel 75 mg Q3weeks* vs Docetaxel 30 mg weekly* vs Mitoxantone* (in patients with metastatic CRPC) *Prednisone given in all 3 arms	**OS:** 19.2 months vs 17.8 months vs 16 months (HR = 0.76; CI, 0.62-0.94; *P* = .009 in docetaxel Q3-weeks arm)	**Neutropenia** Grade 3 or 4: 32%
De Bono et al[34]	2010	Cabazitaxel + prednisone vs Mitoxantrone + prednisone (in patients with CRPC who progressed on docetaxel)	**Median PFS:** 2.8 months vs 1.4 months **Median OS:** 15.1 vs 12.7 months (HR = 0·74; CI, 0·64-0·86; *P* <.0001)	**Neutropenia** Grade 3: 82% All grades: 94% **Diarrhea** Grade 3: 6% All grades: 47%
Gravis et al[47]	2013	Docetaxel 75 mg/m^2 + ADT vs ADT alone (in patients with metastatic non-castrate prostate cancer)	**Median OS:** 58.9 months in docetaxel + ADT arm vs 54.2 months in ADT-only arm. (HR = 1·01; CI, 0·75-1·3; *P* =.955)	**Neutropenia** Grade 3 or 4: 32% Febrile neutropenia: 7%
Sweeney et al[48]	2014	Docetaxel 75 mg/m^2 + ADT vs ADT alone (in patients with newly diagnosed metastatic castration-sensitive prostate cancer)	**OS:** 57.6 months in docetaxel + ADT arm vs 44 months in ADT arm (HR = 0.60; CI, 0.45-0.81 *P* = .0003)	Febrile neutropenia: 6%

ADT indicates androgen-deprivation therapy; CI, confidence interval; CRPC, castration-resistant prostate cancer; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

of cabazitaxel in docetaxel-refractory mCRPC.[34]

Sternberg et al[35] studied satraplatin, a newer oral platinum drug in patients who progressed after 1 prior chemotherapy regimen. In the phase 3 SPARC trial, 950 patients with mCRPC were randomized 2:1 to receive either oral satraplatin 80 mg/m^2 on days 1 to 5 of a 35-day cycle and prednisone 5 mg twice daily, or placebo and prednisone 5 mg twice daily. Primary end points of the study were PFS and OS, and the secondary end point was time to pain progression. After a median follow-up of 29 and 39 weeks in the satraplatin and placebo arms, respectively, no difference in OS was seen between the satraplatin and placebo arms (HR = 0.98; 95% CI, 0.84-1.15; *P* = .80). However, patients who were treated with satraplatin had delayed progression of disease and delayed pain progression.

Cabazitaxel

Cabazitaxel, a semi-synthetic newer taxane, was shown to be active in docetaxel-refractory prostate cancer.[34] In the randomized phase 3 TROPIC trial, 755 patients with CRPC who had progressed on docetaxel were assigned to receive mitoxantrone 12 mg/m^2 intravenously plus prednisone 10 mg or cabazitaxel 25 mg/m^2 intravenously every 3 weeks plus prednisone 10 mg. The median survival was 15.1 months (95% CI, 14.1-16.3) in the cabazitaxel arm and 12.7 months (95% CI, 11.6-13.7) in the mitoxantrone arm, with a HR for death of 0.70 for the cabazitaxel arm (95% CI, 0.59-0.83; *P*<.0001). Toxicity in the cabazitaxel arm was almost exclusively hematologic, with more grade 3 neutropenia, anemia, and thrombocytopenia compared with the mitoxantrone arm. There were 10 deaths from neutropenic fever and diarrhea early in the study, but once granulocyte colony-stimulating fac-

tor (G-CSF) prophylaxis was implemented, there were no further deaths. Based on the TROPIC trial data, cabazitaxel with G-CSF support is currently approved as a second-line chemotherapy in patients who have progressed with docetaxel.

Adjuvant and Neoadjuvant Chemotherapy

Unlike breast cancer, the role of neoadjuvant and adjuvant chemotherapy is not well established in treatment of prostate cancer. Small phase 2 studies have attempted to study the role of chemotherapeutic agents such as single-agent docetaxel and combination therapy such as docetaxel and estramustine, and estramustine and etoposide in the neoadjuvant setting.[36-39] These trials have noted that neoadjuvant chemotherapy may have a role in treatment of high-risk or locally advanced prostate cancer, and may improve treatment outcomes. However, the benefit of neoadjuvant chemotherapy is yet to be demonstrated in a randomized phase 3 trial.

There is a paucity of data on the benefit of adjuvant chemotherapy in the treatment of prostate cancer. The RTOG 9202 trial, which compared androgen suppression (AS) and radiation therapy (RT) versus AS and RT followed by chemotherapy with paclitaxel, estramustine, and etoposide (TEE) for localized, high-risk prostate cancer, showed increased toxicity with no OS benefit.[40,41] Final results of the completed SWOG 9921 randomized trial comparing adjuvant therapy with ADT alone or in combination with mitoxantrone chemotherapy are awaited, and may provide further clarity about the role of adjuvant chemotherapy in prostate cancer.[42]

Androgen-Sensitive Metastatic Prostate Cancer

Hormonal therapy is the first-line treatment for patients with newly diagnosed metastatic disease. It is well established that chemotherapy has a role in the treatment of metastatic prostate cancer in patients who progress on hormonal treatment (ie, CRPC).[28] Its use in rising PSA after local therapy (biochemical relapse) is more controversial but still commonly used. Clinical research trials have attempted to explore the role of chemotherapy in such settings.

Small phase 2 and 3 studies have explored the role of early chemotherapy (either alone or with ADT) in patients with biochemical relapse after local therapy with either radiation or surgery.[43-45] These trials showed that chemotherapy was active as defined by measurable PSA declines in the first-line setting for biochemical relapse.

There are more-extensive but conflicting data available on the role of chemotherapy in combination with hormonal therapy in the metastatic setting. In a phase 3 trial with 286 patients, Millikan et al[46] studied the role of chemo-hormonal treatment with three 8-week cycles of ketoconazole and doxorubicin alternating with vinblastine and estramustine, in addition to standard ADT compared with standard ADT alone. After a median follow-up of 6.4 years, no statistically significant OS difference was noted between the 2 groups (although the study was criticized for not using docetaxel-based chemotherapy).

In the phase 3, multicenter, randomized, controlled GETUG-AFU 15 trial, Gravis and colleagues[47] compared docetaxel plus ADT with standard ADT in patients with metastatic noncastration prostate cancer.[47] After a median follow-up of 50 months, the difference between median OS of the 2 arms was not statistically significant (58.9 months in the ADT-plus-docetaxel group vs 54.2 months in the ADT-alone group; HR = 1.01; 95% CI, 0.75-1.36; P = .955). Interestingly, the docetaxel-plus-ADT arm compared with the ADT-alone arm had a clear clinical median PFS (23.5 vs 15.4 months; HR = 0.75; 95% CI, 0.59-0.94; P = .015) and biochemical median PFS advantage (22.9 months vs 12.9 months; HR = 0.72; 95% CI, 0.57-0.91; P =.005).

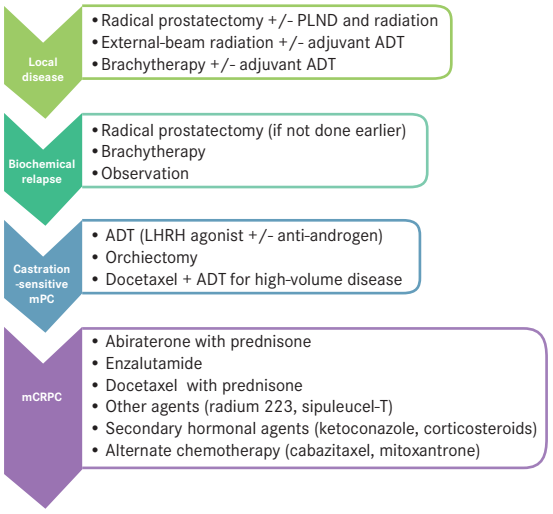
At the 2014 American Society of Clinical Oncology (ASCO) Annual Meeting, Sweeney et al[48] presented preliminary data on the CHAARTED trial, which showed impressive results on the role of chemo-hormonal treatment in castration-sensitive patients. In this trial, 790 men with newly diagnosed metastatic prostate cancer were randomly assigned to receive either ADT alone or ADT in combination with docetaxel, dosed at 75 mg/m^2 every 3 weeks for 6 cycles within 4 months of starting ADT. Patients in the docetaxel arm were continued on ADT alone after completing 6 cycles.

The primary end point of this study was OS. In a planned interim analysis done in October 2013, the study met the criteria for significance and its primary end point (OS) by a large margin.[48] At a median follow-up of 29 months, the median OS was 57.6 months in the ADT-plus-docetaxel group vs 44 months in the ADT group (HR = 0.61; P =.0003). The randomization was stratified by low-volume and high-volume disease based on disease burden. Among 520 patients classified as having high-volume disease due to visceral metastases and/or 4 or more bone metastases, adding docetaxel to ADT improved median OS by 17 months (OS, 49 months in the ADT + docetaxel arm vs 32 months in the ADT-alone arm; HR = 0.60; 95% CI, 0.45-0.81). In patients with low-volume disease, the median OS has not yet been reached due to low mortality (HR = 0.63; 95% CI, 0.34-1.17; P = .14), and longer follow-up will be needed to assess OS in this subgroup. The median time to clinical progression was noted to be 33 months in the study arm compared with 20 months in the ADT-alone arm. Also, the median time to CRPC was significantly longer in the docetaxel-plus-ADT arm compared with the ADT-alone arm (20.7 months vs14.7 months; HR = 0.56; 95% CI, 0.44-0.70; P <.0001). The docetaxel-plus-ADT combination was well tolerated, with febrile neutropenia noted in 6% of subjects, sensory neuropathy in 1%, and motor neuropathy in 1%. Final data on OS, toxicity profile, and long-term follow-up are currently pending.

Non-Cytotoxic Agents for Treatment of CRPC—Recent Advancements

Within the past 3 years, multiple newer drugs have been approved

FIGURE 2. Therapeutic Options for the Treatment of Prostate Cancer



ADT indicates androgen-deprivation therapy; LHRH, luteinizing hormone-releasing hormone; mCRPC, metastatic castration-resistant prostate cancer; mPC, metastatic prostate cancer; PLND, pelvic lymph node dissection.

for treatment of CRPC (**Figure 2**). Hormonal agents such as abiraterone acetate and enzalutamide have shown significant efficacy in patients with CRPC who were docetaxel-naïve; these agents are approved by the FDA in this setting.[49,50] Sipuleucel-T, a cancer vaccine (immunotherapy) has shown OS benefit in patients with mCRPC and is FDA-approved in patients with asymptomatic or minimally symptomatic disease.[51] Similarly, radium 223, a targeted alpha emitter that selectively binds to areas of increased bone turnover in bone metastases, has shown improved OS in patients with CRPC with bony metastasis. The FDA has approved this drug for treating patients with CRPC with symptomatic bony metastasis (without visceral metastasis).[52]

Ongoing Trials and Future Trends

The advent of these newer drugs with better AE profiles has decreased the upfront usage of docetaxel in the treatment of CRPC. In addition to its effect on cell division, recent data suggest that docetaxel exhibits anti-androgen effects by impairing androgen receptor (AR) signaling and activity.[53-55] This AR inhibitory effect of docetaxel (and other taxanes) plays a key role in its antitumor activity in prostate cancer, and has led to a flurry of research on docetaxel in settings other than CRPC.

Large phase 3 trials are looking at the role of docetaxel in the adjuvant, neoadjuvant, and castration-naïve settings. Eastham and colleagues, in their phase 3 trial (CALGB90203), are investigating the benefit of neoadjuvant docetaxel and ADT prior to radical prostatectomy compared with prostatectomy alone in patients with high-risk or locally advanced prostate cancer. This study is expected to be completed in the summer of 2018. The ongoing Radiation Therapy Oncology Group (NCT00288080) phase 3 trial in patients with localized prostate cancer comparing combined ADT followed by 8 weeks of radiation with combined ADT followed by 8 weeks of radiation and 6 courses of docetaxel has finished recruiting.[56] The STAMPEDE trial (NCT00268476) is studying the role of upfront docetaxel plus ADT compared with several other standard therapies in newly diagnosed metastatic prostate cancer.[57] Once these studies are completed and published, we will have better guidance on the benefits of using docetaxel early in the treatment of prostate cancer to improve outcomes.

Researchers also are exploring newer cytotoxic agents in the treatment of prostate cancer. Multiple phase 2 trials with newer chemotherapeutic drugs such as tesetaxel (a novel oral taxane),[58] carfilzomib (a second-generation proteasome inhibitor),[59] and olaparib (a PARP inhibitor, particularly in BRCA mutation-associated cases),[60] and immune-modulating agents such as ipilimumab (a monoclonal antibody targeting CTLA-4 receptor),[61] are ongoing in patients with mCRPC, and may result in newer therapeutic options in the future.

Conclusion

Chemotherapeutic agents have evolved significantly in the last 2 decades, from palliative drugs to the drugs that improve OS in the treatment of CRPC. With the exception of docetaxel in the first-line setting and cabazitaxel in the second-line setting, no other chemotherapy has shown a significant OS advantage in the treatment of CRPC. Chemotherapy drugs come with their unique AE profile, and the success of newer hormonal agents such as abiraterone acetate, enzalutamide, and other palliative agents has diminished the use of upfront chemotherapy in the realm of CRPC.

Nevertheless, extensive research is ongoing now to establish the role of early chemotherapy in improving the response obtained from current standards of care. Recently, the CHAART-ED trial demonstrated that the early use of docetaxel along with ADT yields a significantly greater OS advantage in patients with mCRPC.

Chemotherapy is an important tool for the treatment of prostate cancer and will likely have a greater role in the future. The results from current trials on the timing and efficacy of chemotherapy in the neoadjuvant, adjuvant, and castration-sensitive metastatic prostate cancer settings might potentially change current clinical practice for the treatment of prostate cancer.

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tourinary Committee for US Oncology Research.

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