Upfront Chemotherapy for Metastatic Prostate Cancer

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In this review, we describe the historical data for chemotherapy in the perioperative and metastatic prostate cancer settings, and the recent trials that are changing the paradigm in support of docetaxel in the upfront setting.

**Introduction**

Androgen deprivation therapy (ADT) has been the standard initial treatment for metastatic hormone-sensitive prostate cancer (mHSPC). Docetaxel, a chemotherapeutic agent approved in 2004 based on data from the TAX 327 and the Southwest Oncology Group (SWOG) S9916 clinical trials, was the first medical therapy to demonstrate an overall survival benefit for patients with metastatic castration-resistant prostate cancer (mCRPC).[1,2] Since 2010, the successive approvals of new agents with incremental improvements in overall survival (sipuleucel-T, abiraterone acetate, enzalutamide) have dramatically changed the treatment paradigm for mCRPC, leading to many patients delaying or never receiving cytotoxic chemotherapy. Table 1 summarizes the aggregate trial data for patients with metastatic prostate cancer, based on survival reported from individual registration trials.[1-11]

Sweeney et al recently published the results of the Eastern Cooperative Oncology Group (ECOG) E3805 CHAARTED (ChemoHormonal Therapy Versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer) trial, which evaluated the addition of docetaxel to ADT for the first-line treatment of men with untreated mHSPC.[12] The results were overwhelmingly positive and are changing the treatment paradigm for chemotherapy-eligible patients with metastatic prostate cancer.

**Traditional Role of Cytotoxic Chemotherapy in Metastatic Prostate Cancer**

Mitoxantrone, docetaxel, and cabazitaxel are three chemotherapeutic agents currently approved for the treatment of metastatic prostate cancer, after castration resistance has developed. In all cases, the use of these agents has been limited in practice to the later castration-resistant stages of the disease.

Mitoxantrone, a synthetic anthracenedione, was approved in 1996 for the treatment of mCRPC based on the palliative endpoint of pain improvement.[13] In the pivotal study of 161 patients with mCRPC who were randomly assigned to receive mitoxantrone and prednisone, compared with prednisone alone, 38% of patients in the chemotherapy arm vs 21% in the prednisone-alone arm had a marked reduction in severe bone pain. This improvement in pain was durable, with a median duration of pain relief of 8 months for the chemotherapy arm vs 2 months for the prednisone-alone arm. However, there was no difference in overall survival between the two treatment groups.

Docetaxel is a semisynthetic taxane with a twofold mechanism of antineoplastic activity: inhibition of microtubular depolymerization, and attenuation of the effects of BCL2 and BCL-xL gene expression.[14] Docetaxel was approved in 2004 for mCRPC, based on data from the TAX 327 study demonstrating an overall survival benefit. The TAX 327 study randomized 1,006 mCRPC patients to one of three treatment arms (mitoxantrone + prednisone; weekly docetaxel + prednisone; or docetaxel once every 3 weeks + prednisone). Compared with the mitoxantrone arm, the group receiving docetaxel every 3 weeks demonstrated a statistically significant survival advantage (median survival, 18.9 vs 16.5 months; hazard ratio [HR], 0.76 [95% confidence interval (CI), 0.62–0.94]; P = .009).[1] The survival benefit persisted with extended follow-up (median survival, 19.2 vs 16.3 months; P = .004).[2] The weekly docetaxel arm did not demonstrate an advantage in overall survival over the control arm. Treatment with docetaxel also led to improved prostate-specific antigen (PSA) responses, reductions in pain, and improvements in quality of life.

Cabazitaxel, a tubulin-binding taxane with poor affinity for P-glycoprotein, was approved in 2010 for...
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the treatment of mCRPC that has progressed during or after docetaxel-based therapy.[4] The approval was based on the results of the TROPIC study, which randomized 755 mCRPC patients previously treated with docetaxel to receive cabazitaxel plus prednisone or mitoxantrone plus prednisone. There was a statistically significant improvement in overall survival in the cabazitaxel arm compared with the mitoxantrone arm (median survival, 15.1 vs 12.7 months; HR, 0.70 [95% CI, 0.59–0.83]; P < .0001). There were also improvements in progression-free survival (PFS; 2.8 vs 1.4 months), as well as in RECIST (Response Evaluation Criteria in Solid Tumors) response rates (14.4% vs 4.4%; P = .0005) and PSA response rates (39.2% vs 17.8%; P = .0002) in patients treated with cabazitaxel compared with mitoxantrone.

Role of Perioperative or Adjuvant Chemotherapy in Localized Prostate Cancer

Chemotherapy has also been evaluated in the neoadjuvant and adjuvant settings for high-risk localized prostate cancer. Numerous neoadjuvant trials evaluating docetaxel or paclitaxel, alone or in combination with hormone therapy prior to radical prostatectomy, have shown a low rate of pathologic complete responses and mixed toxicity profiles.[15-21] SWOG S9921 was the largest prospective adjuvant trial designed to evaluate the addition of mitoxantrone to ADT vs ADT alone in 983 high-risk prostate cancer patients after radical prostatectomy. Unfortunately, this trial was terminated early after three cases of acute myelogenous leukemia were reported in the mitoxantrone arm.[22] Based on results released for patients treated on the ADT-only arm, the estimated 5-year biochemical failure–free survival was 92.5% (95% CI, 90%-95%) and 5-year overall survival was 95.9% (95% CI, 93.9%-97.9%).[23] The final overall survival results comparing the two arms have not been reported. A pilot French study that randomized 47 patients with high-risk prostate cancer to receive adjuvant ADT with or without weekly paclitaxel treatments for 8 weeks reported no impact on quality of life or symptoms post-prostatectomy; however, survival data have not been reported.[24] The use of chemotherapy in the neoadjuvant and adjuvant settings remains investigational and is not currently the standard of care. The Cancer and Leukemia Group B (CALGB) 90203 trial (Preoperative Use of Neoadjuvant ChemoHormonal Therapy [PUNCH]; ClinicalTrials.gov identifier: NCT00430183) is a phase III neoadjuvant trial that randomized patients with clinically localized high-risk prostate cancer who have opted for radical prostatectomy to receive neoadjuvant ADT and docetaxel prior to surgery vs surgery alone. Other ongoing trials in high-risk or locally advanced patients include a phase I study of cabazitaxel and adjuvant radiation (ClinicalTrials.gov identifier: NCT01650285), a phase II study of neoadjuvant cabazitaxel and ADT followed by salvage surgery for patients with biopsy-proven recurrence after initial definitive radiotherapy (ClinicalTrials.gov identifier: NCT01531205), a phase II study of radiotherapy and ADT with or without docetaxel (ClinicalTrials.gov identifier: NCT00116142), the phase III GETUG 12 trial of adjuvant ADT with or without docetaxel and estramustine (ClinicalTrials.gov identifier: NCT00055731), and the Veterans Affairs Cooperative Study #553 that is comparing early adjuvant docetaxel vs standard of care in high-risk post-prostatectomy patients (ClinicalTrials.gov identifier: NCT00132301).

New Data on Docetaxel for mHSPC

The use of chemotherapy in the upfront metastatic hormone-sensitive setting has not been standard practice due to the initial evaluation of cytotoxic agents in the metastatic castration-resistant setting, patient and physician concerns of toxicity, the impact on quality of life, the increasing availability of other hormonal and immunotherapeutic options, and the lack of survival data for chemotherapy in the metastatic hormone-sensitive setting—that is, until now. The recent data reported from the CHAARTED, GETUG-AFU 15, and STAMPEDE (Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy) clinical trials has shed new light on the role of upfront docetaxel in advanced or mHSPC (Table 2).

CHAARTED trial

The phase III CHAARTED clinical trial evaluated whether the addition of docetaxel at the start of ADT for mHSPC would improve overall survival. Between July 2006 and December 2012, 790 patients with mHSPC were randomized to receive ADT plus 6 cycles of docetaxel vs ADT alone. Concomitant chemohormonal therapy was associated with a significant overall survival improvement of 13.6 months (57.6 vs 44 months; HR, 0.61 [95% CI, 0.47–0.80]; P < .001) compared with ADT alone.[12]
This benefit was observed in the overall intent-to-treat population, and was maintained in subset analyses of both patients with high-volume (defined as visceral metastases or ≥ 4 bone lesions with ≥ 1 beyond the vertebral bodies or pelvis) and low-volume disease (HR, 0.60 for both groups). The median time to development of CRPC (biochemical, symptomatic, or radiographic progression) was 20.2 months with combination therapy and 11.7 months with ADT alone (HR, 0.61 [95% CI, 0.51–0.72]; \( P < .001 \)). The median time to clinical progression (increasing symptoms of bone metastases or radiographic progression) was 33 months for combination therapy vs 19.8 months for ADT alone (HR, 0.61 [95% CI, 0.50–0.75]; \( P < .001 \)). PSA levels less than 0.2 ng/mL at 12 months (27.7% vs 16.8%; \( P < .001 \)) improved in the patients in the chemohormonal therapy arm compared with the ADT-alone arm. The benefit of adding docetaxel to ADT was consistently seen across all other subgroups, including age younger than 70 years vs ≥ 70 years; ECOG score of 0 vs 1–2; race (white vs non-white); type of metastases (visceral with or without bone metastases vs bone-only metastases); Gleason score of less than 8 vs ≥ 8; previous local therapy; duration of combined androgen blockade > 30 days vs ≤ 30 days; and therapy for skeletal-related event at the time of ADT initiation.

In the combination therapy arm, the rate of grade 3/4 febrile neutropenia was 6.2% and the rate of grade 3/4 infection with neutropenia was 2.3%. In addition, 86% of patients in the combination arm who started on ADT completed the prescribed 6 cycles of docetaxel, with 74% of all patients in this arm completing 6 cycles without any dose modification required. Among the 393 patients in the ADT-only arm, 287 received subsequent therapies (137 [35%] of whom received docetaxel) in the castration-resistant setting. The magnitude of the survival benefits across all subgroups seen in this study supports the use of upfront docetaxel administration based on the significant improvement in overall survival with good tolerance overall.

GETUG-AFU 15 trial

GETUG-AFU 15 was a phase III study conducted in France and Belgium, which randomized 385 patients (enrolled between October 2004 and December 2008) with metastatic non-CRPC to receive ADT plus 9 cycles of docetaxel vs ADT alone; this was the smallest of the three studies examining upfront chemotherapy.[25] Median biochemical PFS (22.9 vs 12.9 months; HR, 0.72 [95% CI, 0.57–0.91]; \( P = .005 \)), clinical PFS (23.5 vs 15.4 months; HR, 0.75 [95% CI, 0.59–0.94]; \( P = .015 \)), and PSA response rate at 3 months (91% vs 80%; \( P = .0096 \)) and at 6 months (94% vs 84%; \( P = .0185 \)) were all significantly improved in the ADT plus docetaxel group compared with the ADT-alone group. However, median overall survival was not statistically significant between the two groups: 58.9 months in the chemohormonal therapy group and 54.2 months in the ADT group (HR, 1.01 [95% CI, 0.75–1.36]). On subgroup analysis, median overall survival did not differ in the two treatment groups for any subgroup. The median number of docetaxel cycles was 8: 93 patients (48%) received the planned 9 cycles of docetaxel; 39 patients (20%) discontinued docetaxel because of toxicity; and 21 patients (11%) had dose reduction of docetaxel. At the time of castration resistance, 120 (62%) of 193 patients in the ADT-alone arm and 54 (28%) of 192 patients in the combination arm received subsequent docetaxel. In an updated analysis with additional follow-up, there was still no statistically significant difference in overall survival in the chemohormonal therapy group compared with the ADT-alone group (60.9 vs 46.5 months; HR, 0.9 [95% CI, 0.7–1.2]; \( P = .44 \)), but a trend towards benefit with the addition of docetaxel was noted. Subset analyses of high-volume vs low-volume disease (using the same criteria as the CHAARTED study) also did not show any statistical difference in overall survival between the two groups.[26]
How Has the Role of Docetaxel Changed in Prostate Cancer Therapy?

Over a decade ago, docetaxel chemotherapy was the first treatment to improve survival in patients with metastatic castration-resistant prostate cancer (mCRPC). In 2015, docetaxel has again changed the standard of care, this time in metastatic hormone-sensitive prostate cancer (mHSPC). The strongly positive survival results from CHAARTED and STAMPEDE, two large, well-powered, international studies that evaluated the effect of 6 cycles of docetaxel chemotherapy in mHSPC patients, has now shifted the use of chemotherapy to the time of diagnosis of metastatic disease. In this setting, docetaxel is associated with additional survival durations ranging from 13 to 22 months. In comparison, the median additional survival from docetaxel in mCRPC patients was only 2 to 3 months. This dramatic benefit suggests that the question we should be asking ourselves is not, “Should we give docetaxel to this newly diagnosed metastatic patient?” But rather, “Is there any reason not to give chemotherapy?”

How Do We Move Forward Based on the Trial Results?

Questions do remain. For instance, most of the patients in CHAARTED and STAMPEDE were initially diagnosed with metastatic disease. Is the benefit clearly the same in a patient who has been followed for years after surgery or radiation and has a new metastasis? Another unknown is whether newer androgen receptor-targeted therapies such as enzalutamide and abiraterone acetate could have the same benefit, given their comparable activity in the CRPC setting. Finally, toxicity will need to be assessed closely in the “real-world” setting, since higher rates of febrile neutropenia have been reported, particularly in the STAMPEDE trial, which means that caution is needed in considering docetaxel in the general population. For now, though, all patients with mHSPC should be considered for 6 cycles of docetaxel chemotherapy.

STAMPEDE trial

STAMPEDE is a multi-stage, multi-arm, randomized controlled trial that is evaluating the effect of the addition of various agents (eg, docetaxel, zoledronic acid, celecoxib, abiraterone, enzalutamide, and radiotherapy) to ADT in men with high-risk nonmetastatic or mHSPC. This ongoing trial commenced in 2005 and has enrolled almost 7,000 patients from more than 100 centers across the United Kingdom and Switzerland. The survival data from 917 patients with newly diagnosed M1 disease in the control arm have recently been reported.[27] Among this group of M1 prostate cancer patients, there was a median age of 66 years, a median PSA of 112 ng/mL, 62% with bone-only metastases, and 26% with both bone and soft tissue (distant lymph node) metastases; the median failure-free survival was 11 months and median overall survival was a disappointing 42 months, despite active treatments being available in the castration-resistant setting. The first reported overall survival results from 2,962 patients in four study arms (ADT alone [control arm]; 6 cycles of docetaxel + ADT; 2 years of zoledronic acid + ADT; and docetaxel + zoledronic acid + ADT) were released at the 2015 American Society of Clinical Oncology (ASCO) Annual Meeting. There was a significant survival benefit observed with the addition of docetaxel to ADT.[28] In the overall study population, including all patients with high-risk nonmetastatic or regional (lymph node)
metastatic (M0) and distant metastatic (M1) prostate cancer, the median overall survival was improved by 10 months in the docetaxel arm compared with the standard-of-care arm (77 vs 67 months; HR, 0.76 [95% CI, 0.63–0.91]; P = .003). In the subset of patients with M1 metastatic disease, the improvement in overall survival was a remarkable 22 months (65 vs 43 months; HR, 0.73 [95% CI, 0.59–0.89]; P = .002). In contrast, there was no survival advantage for the M0 subset of patients (HR, 1.01 [95% CI, 0.65–1.56]). However, the addition of docetaxel to ADT significantly improved the failure-free survival in both M0 (HR, 0.57 [95% CI, 0.42–0.76]) and M1 patients (HR, 0.62 [95% CI, 0.54–0.73]). The addition of zoledronic acid to ADT did not improve survival, and the combination of zoledronic acid with docetaxel and ADT did not have any discernable additional benefit compared with the addition of docetaxel alone to ADT. The investigators concluded that docetaxel should be considered for men with newly diagnosed metastatic disease given the substantial improvement in overall survival, and for selected men with high-risk nonmetastatic disease due to the significant prolongation of failure-free survival.

**Discussion**

There are currently three large phase III clinical trials that have evaluated the addition of docetaxel to ADT in the upfront treatment of mHSPC. The CHAARTED and STAMPEDE trials have shown significant improvement in overall survival, while GETUG-AFU 15 showed no statistical difference. One hypothesis postulated to explain the survival difference of docetaxel use based on its timing in the disease course is that there may be some differences in the pharmacokinetics of docetaxel in patients who have hormone-sensitive disease and castration-resistant disease. In a small study of 10 noncastrated and 20 castrated prostate cancer patients, in which “castrated” was defined as having progressed to an androgen-independent state, docetaxel clearance was increased by approximately 100% in the castrated men and was associated with a twofold reduction in area under the curve (P = .0001).[29] These pharmacokinetic differences indicating higher docetaxel exposure in non-castration-resistant patients may explain the overall survival benefit in the hormone-sensitive setting. Further studies are needed to confirm this observation.

The survival difference with the addition of chemotherapy in the upfront setting may also be explained by the effect on time to development of castration resistance. Historically, prostate cancers respond quite well initially to ADT, leading to remissions lasting 2 to 3 years before development of castration resistance.[30] The 8.5-month difference in time to castration resistance in the CHAARTED study (20.2 months for the combination ADT + chemotherapy arm and 11.7 months for the ADT-alone arm) is a much shorter duration of hormone-sensitive disease than would be expected, and likely reflects mainly biochemical progression based on the definition used in the study. The time to clinical, or radiographic, progression in CHAARTED was closer to historical reports: 33.0 vs 19.8 months in the combination and ADT arms, respectively. This 13.2-month difference in time to clinical progression between the two groups is almost the same as the overall survival difference of 13.6 months, perhaps indicating that this difference in time to progression and the delay that docetaxel provides in this stage of progression may account for the survival advantage. From a patient perspective, this is important, since men are, in general, fairly asymptomatic early in the course of their disease, and there is likely an improvement in overall quality of life by delaying the progression to symptomatic disease.

The CHAARTED and STAMPEDE studies showed significant improvements in both PFS and overall survival, particularly in patients with high-volume disease (Table 2). In both studies, only a fraction of patients in the ADT-alone arm received subsequent docetaxel (35% and 41% for the CHAARTED and STAMPEDE studies, respectively). This is an important point, since all the patients in these studies were eligible for chemotherapy by definition at the start of the trials. In contrast, in the GETUG-AFU 15 study, while there was a significant improvement in PFS, there was no significant benefit seen in overall survival. The GETUG-AFU 15 study completed enrollment prior to the availability of abiraterone acetate or enzalutamide; therefore, the majority of patients (62%) in the ADT-alone arm subsequently received docetaxel in the castration-resistant setting. This may have confounded the results and contributed to the overall negative survival findings.

In addition, the low percentage of patients receiving subsequent docetaxel in the CHAARTED and STAMPEDE ADT-alone arms likely reflects current real-world clinical practice. In the current era in which noncytotoxic treatments (abiraterone, enzalutamide, sipuleucel-T, radium-223) have a more favorable toxicity profile and survival benefit, patients and clinicians are generally deferring cytotoxic chemotherapy until after progression on these noncytotoxic agents. As a result, many patients do not receive docetaxel when their cancer has progressed after multiple agents due in part...
to a potential reduction in their performance status from disease progression. The remarkable survival results of the CHAARTED and STAMPEDE studies for patients receiving upfront docetaxel for mHSPC will change the current paradigm to allow many more patients to receive chemotherapy. The adoption of upfront chemotherapy plus hormone therapy for newly metastatic hormone-naive prostate cancer requires a multidisciplinary approach, in which medical oncologists are involved early in the course of the patient’s disease, at the time of the initiation of ADT and with the recognition of metastatic disease. In this context, medical oncologists can meet with newly diagnosed metastatic prostate cancer patients and determine their eligibility and interest in chemotherapy. Given the CHAARTED study findings that showed a survival benefit in the intent-to-treat population with a very similar HR for both the high- and low-volume patients, along with the findings of the STAMPEDE study that showed a survival benefit in metastatic but not M0 or locally confined/high-risk patients, we would recommend consideration of the upfront combined approach in properly selected M1 patients with hormone sensitivity. There are currently insufficient data available to support the routine upfront use of docetaxel for patients with regional lymph node-only disease.

The results of these studies raise several new questions: What is the optimal timing of chemotherapy after the initiation of ADT in these patients? Should ADT be delayed in those with biochemical failure but no radiographic disease in deference to using ADT with chemotherapy after the development of metastatic disease radiographically? What role might the new highly active hormonal treatments (eg, abiraterone and enzalutamide) have in the upfront metastatic hormone-naive setting? These and other questions will be the focus of planned and future clinical trials.

Conclusion

The results of the CHAARTED and STAMPEDE trials have created a new paradigm for the treatment of newly diagnosed mHSPC patients. The magnitude of the survival benefit observed with docetaxel in this setting far exceeds that of any novel agent approved for mCRPC in the past decade. Optimal patient selection and a multidisciplinary approach with early involvement of medical oncologists are important components of implementing this new paradigm in the treatment of metastatic prostate cancer.

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Table 1. Survival Improvements of Specific Agents in Metastatic Prostate Cancer

Table 2. Similarities and Differences Between CHAARTED, GETUG-AFU 15, ...

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