Review Article

Targeting Metastatic Hormone Sensitive Prostate Cancer: Chemohormonal Therapy and New Combinatorial Approaches

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Abbreviations and Acronyms

ADT = androgen deprivation therapy

AR = androgen receptor

CHAARTED = Chemohormonal Therapy versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer

CRPC = castration resistant PC

GETUG—AFU = Groupe d'Étude des Tumeurs Uro-Genital and Association Française d'Urologie trial

HSPC = hormone sensitive PC

mHSPC = metastatic HSPC

PC = prostate cancer

PSA = prostate specific antigen

QOL = quality of life

STAMPEDE = Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy

Purpose: Androgen deprivation therapy alone has been the standard of care for metastatic hormone sensitive prostate cancer for the last 75 years. This review focuses on recent trials and mechanisms which highlight the new paradigm of combining androgen deprivation therapy with other agents, changing the treatment of patients with prostate cancer who have advanced disease.

Materials and Methods: We searched the peer reviewed literature on the PubMed® and Web of Science® databases through January 2018 using the key words, "metastatic hormone sensitive prostate cancer," "metastatic castration sensitive prostate cancer," "docetaxel," "abiraterone" and "senescence in cancer." ClinicalTrials.gov was queried for ongoing studies. Relevant data recently presented at major urology and medical oncology meetings were also evaluated.

Results: Recently published, phase III trials using androgen deprivation therapy combinations for metastatic hormone sensitive prostate cancer can be broadly grouped into chemohormonal studies (docetaxel) or trials of androgen signaling inhibitors. The CHAARTED (Chemohormonal Therapy versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer) and STAMPEDE (Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy) studies showed a survival advantage when combining androgen deprivation therapy with chemotherapy, as well as increased time to progression to castration resistant status. The abiraterone arm of the STAMPEDE and LATITUDE trials, which analyzed combining androgen deprivation therapy with abiraterone, revealed improved overall and progression-free survival. Androgen deprivation therapy generates a number of phenotypes in resistant cancer cells, including quiescence, autophagy and cellular senescence. Senescent cells represent a metabolic target for synergistic lethality with drugs such as metformin. Ongoing trials are under way to examine the effect of combining newer antiandrogens and novel drugs with androgen deprivation therapy in patients with metastatic hormone sensitive prostate cancer.

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Conclusions: Combination therapy has evolved as the standard of care for metastatic hormone sensitive prostate cancer. The ideal combination is tailored to patients after individualized counseling taking into account general health and comorbid illness status.

Key Words: prostatic neoplasms, castration-resistant; neoplasm metastasis; drug therapy, combination; antineoplastic agents; cellular senescence

Prostate cancer is the most common cancer in males with an estimated new case incidence of 164,690 and an estimated mortality of 29,430 expected in 2018. Despite an overall 5-year survival rate of 98.2%, mHSPC has a dismal 30% 5-year survival rate.[1] Conventional treatment of mHSPC has been ADT since the landmark discovery by Huggins and Hodges in 1941 demonstrating the hormonal sensitivity of PC.[2] Metastatic HSPC treated with ADT transitions to the CRPC stage with a median survival of approximately 3 years.[2] Progression to CRPC is associated with a deterioration in QOL. In the recently concluded STAMPEDE trial patients were found to spend three-quarters of overall survival after the mHSPC diagnosis in the CRPC state, highlighting the significant alteration in the natural history of the disease with newer treatments.[3] Treatment continues to evolve with a focus on disease management at earlier time points.

Approaches to improve the response rate to ADT or decrease side effects have included intermittent hormone therapy, use of an antiandrogen with medical or surgical castration, or antiandrogens alone.[4] An analysis of these trials detailed the minimal benefits of these approaches, including only 2% to 3% improvement in 5-year survival with a wide range of uncertainty.[4] For a number of years researchers had considered earlier application of cytotoxic therapy in an effort to delay progression to castrate disease. The addition of chemotherapy to ADT was tested in the last 30 years and this approach was used in a number of published randomized trials, as summarized by Millikan et al.[5] However, the lack of cytotoxic therapy, which improved survival in CRPC cases, led to minimal advances. In CRPC more recently docetaxel chemotherapy resulted in an incremental 2.5-month improvement in median survival, leading to its approval in 2004.[6] These findings lead to the initiation of trials earlier in the disease in patients with a larger disease burden at ADT initiation.

ADT induces a number of unique responses in prostate cancer cells, of which some lead to cellular persistence and the development of castration resistance. Recent phase III trials have demonstrated striking improvements in patient survival with combined ADT and docetaxel as well as ADT and androgen synthesis inhibitors. The synergistic targeting of hormonally sensitive prostate cancer with ADT combined with other novel agents is a new chapter in the evolution of prostate cancer treatment. These trials and new approaches are reviewed in this study, emphasizing that combination therapy is now the standard of care in patients with mHSPC.

METHODS

We performed PubMed and Web of Science database searches of the peer reviewed mHSPC literature on the mechanisms of cellular persistence after ADT as well as combination therapies that use ADT with another therapeutic agent (fig. 1). Original studies of this subject as well as a small number of reviews were analyzed for strengths and weaknesses. We provide a comprehensive review of prospective, phase III trials of combination therapy with ADT in the setting of mHSPC, the synergy mechanism, side effects and QOL. The mechanisms of cellular persistence after ADT are also discussed with special emphasis on senescence. Combination therapies ongoing and to be considered in the near future are examined.

RESULTS

Metastatic Hormone Sensitive Prostate Cancer

Chemohormonal Therapy Trials. Early studies of chemotherapy combined with ADT were less optimistic, in part due to toxicity and the lack of active agents. Millikan et al performed a phase III trial in 286 patients with mHSPC who received 3, 8-week cycles of ketoconazole and doxorubicin alternating with vinblastine and estramustine, given in addition to standard ADT vs ADT alone.[5] No difference in time to progression or overall survival was noted. Furthermore, 51% of patients experienced grade 3 or worse adverse events, including thromboembolic events. Another trial featured mitomycin, cyclophosphamide, epirubicin and fluorouracil with no improvement in survival.[7] In 2004 improved survival in CRPC with docetaxel chemotherapy subsequently led to consideration of its use at the time of ADT initiation in patients with a higher tumor burden.

The CHAARTED study was the first trial to show that adding 6 cycles of docetaxel 75 mg/m^2 every 3 weeks to standard ADT significantly improved outcomes in men with mHSPC (table 1).[8] The 13.6-month improved overall survival in the chemohormonal group compared to the ADT group (median overall survival 57.6 vs 44 months, HR 0.61, 95% CI 0.47–0.80, p <0.001) represented one of the

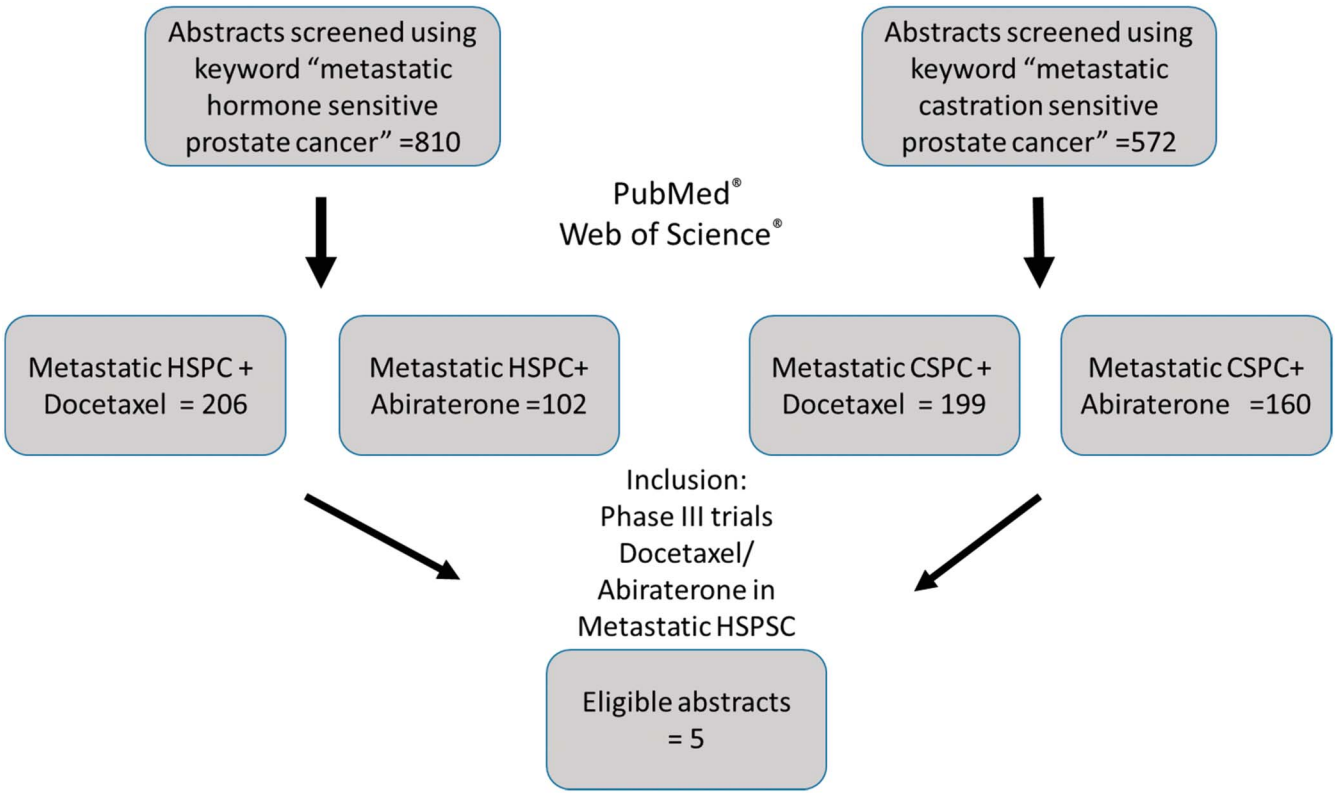

Figure 1. Review criteria used for study selection. *CSPC,* castration sensitive prostate cancer.

largest improvements in survival in patients with advanced PC in the modern era. Time to the CRPC transition was also prolonged in the chemo-hormonal therapy arm (20.2 vs 11.2 months, HR 0.61, 0.51–0.72). On stratified analysis of patients with high volume disease, defined as visceral metastases, or 4 or more bone lesions with at least 1 lesion beyond the vertebral bodies and pelvis, there was almost 17-month improved overall survival, which was not seen for low volume disease (51.2 vs 34.4 months, HR 0.63, 0.50–0.79, p <0.0001). This was attributable to the higher proportion of hormone resistant cells in the high volume disease subpopulation, which contributed to resistance to hormonal manipulation.

The STAMPEDE study uses a unique phase II/III trial design to investigate new agents under the umbrella of a single trial. Additional arms are added to the study as new approaches are designed.[9] Patients were initially stratified into 4 groups which received ADT alone, ADT plus docetaxel, ADT plus zoledronate and ADT plus docetaxel plus zoledronate, respectively. In addition to metastatic disease, the study also included lymph node involvement, high risk locally advanced disease (T3/4 plus Gleason score 8–10, T3/4 plus prostate specific antigen 40 ng/ml or greater or Gleason score 8–10 plus prostate specific antigen 40 ng/ml or greater) and recurrent disease previously treated with definitive local therapy. There was a 10-month improvement

Table 1. *Phase III combination trials with ADT in metastatic hormone sensitive prostate cancer*

	ADT + Docetaxel/ADT			ADT + Abiraterone/ADT	
	GETUG-AFU 15	CHAARTED	STAMPEDE-Docetaxel	LATITUDE	STAMPEDE-Abiraterone
No. pts	192/193	397/393	592/1,184	597/602	960/957
Median age	63/64	64/63	65/65	68/67	67/67
Median survival:					
Overall*	58.9/54.2 Mos	57.6/44 Mos	81/71 Mos	66%/49%	83%/76%
HR (95% CI)	0.88 (0.68–1.14)	0.61 (0.47–0.80)	0.78 (0.66–0.93)	0.62 (0.51–0.76)	0.63 (0.52–0.76)
Progression-free†	22.9/12.9 Mos	20.2/11.7 Mos	37/20 Mos	33/14.8 Mos	75%/45%
HR (95% CI)	0.72 (0.57–0.91)	0.61 (0.51–0.72)	0.61 (0.53–0.70)	0.47 (0.39–0.55)	0.29 (0.25–0.34)

* CHAARTED and STAMPEDE 5-year survival, and LATITUDE and STAMPEDE-Abiraterone 3-year survivor rate with survival in STAMPEDE including M0 (nonmetastatic) and M1 (metastatic) subsets at 60 vs 45 months for STAMPEDE-docetaxel in M1 subset combination and ADT arms, respectively.
† CHAARTED time to CRPC, STAMPEDE clinical, radiographic and biochemical failure-free survival and LATITUDE radiographic survival.

in overall survival in the chemohormonal therapy arm compared to the ADT arm (81 vs 71 months, HR 0.78, 95% CI 0.66–0.93, p = 0.006). The secondary end points of failure-free survival and time to the first skeletal related event were also significantly better in the chemohormonal therapy arm.

A third study using this approach, the GETUG-AFU 15 trial, which also compared chemohormonal therapy to ADT, did not report improved outcomes. However, post hoc analysis of data on the high volume disease subset showed a nonsignificant 20% reduction in death.[10,11] A recent meta-analysis of aggregate data of patients with high volume disease from the CHAARTED and GETUG-AFU 15 trials showed a survival advantage with a pooled HR of 0.68 (95% CI 0.56–0.82, p <0.00).[12] There was also significant heterogeneity in the treatment effect in the combination treatment arm between the high and low volume subgroups (p = 0.017). This suggests that other approaches, notably a biomarker based on tumor genotype, might better inform patient selection for treatment.

In GETUG-AFU and CHAARTED side effects were more common in the chemohormonal therapy arm. The most common grade 3 or greater adverse events in GETUG-AFU and CHAARTED were neutropenia at 32% and 12%, febrile neutropenia at 7% and 6%, and fatigue at 7% and 4%, respectively. In each study there were negligible grade 3 or greater adverse events in the ADT arm. Diarrhea, stomatitis, and motor and sensory neuropathy were the less common adverse effects, which developed in less than 1% of the population in the CHAARTED study. STAMPEDE reported additional toxicity in the chemohormonal therapy arm compared with that of ADT alone (grade 3 or greater adverse events in 52% vs 32% of patients). This was mostly due to toxicity during the first 6 months on trial, when grade 3 or greater adverse events were reported in 36% of the chemohormonal therapy arm vs 17% in the ADT arm. A 1-year analysis of 1,998 patients with available profiles revealed a balanced rate of grade 3 or greater adverse events of 10% in each arm. There were 2 deaths in the chemohormonal therapy arm and 72 patients (13%) discontinued treatment. QOL assessment was done 3, 6, 9 and 12 months after randomization in CHAARTED using the FACT (Functional Assessment of Cancer Therapy)-Prostate score. Although QOL scores with docetaxel decreased at 3 months, it was better at 12 months in patients who received docetaxel vs ADT alone.[13]

Chemohormonal therapy may improve survival because of the existence and emergence of hormonally resistant cellular clones during the CRPC transition. Interestingly, each trial that demonstrated a survival advantage had a time delay between the start of ADT and chemotherapy, including 120 days in CHAARTED and 90 days in STAMPEDE. In GETUG-AFU 15 the patients were required to enroll within 2 months of starting ADT and almost half of them enrolled within 15 days of starting ADT. Some have suggested that this might explain the decreased survival benefit with chemohormonal therapy in this trial. A timed sequence of chemohormonal therapy contributes to maximum synergy by targeting hormone resistant cells when they are most vulnerable.[14] Microtubule targeting chemotherapy inhibited nuclear translocation of androgen receptor in preclinical studies, which also potentially contributes to synergy with ADT.[15]

Combined Androgen Deprivation Therapy and Androgen Synthesis Inhibitors. Abiraterone inhibits cytochrome P-450 CYP17, a critical enzyme in androgen biosynthesis in the testes, adrenal gland and prostate. Its active D4A metabolite contributes to its antitumor effects through blockade of multiple steroidogenic enzymes and antagonism of the androgen receptor.[16] Approval of this drug in the prechemotherapy and post-chemotherapy era led to its application to earlier disease. Resistance to ADT is driven in part by up-regulation of androgen receptor signaling through adrenal androgen production, intratumor testosterone production and modification of androgen receptors.[17] The neoadjuvant combination of abiraterone plus prednisone and ADT markedly reduced the tumor burden in men with newly diagnosed, high risk, localized prostate cancer, suggesting a potential role for inhibiting extragonadal androgen biosynthesis before the emergence of resistant clones.[18] These findings led to 2 randomized, phase III trials testing the efficacy of abiraterone and ADT in mHSPC.

In STAMPEDE-Abiraterone the investigators reported outcomes of the combination of abiraterone and prednisone at the time of ADT initiation.[19] They used a multistage, multi-arm setting similar to that of previous trials enrolling patients with newly diagnosed metastatic, node positive or high risk locally advanced disease. Patients who relapsed with high risk features after previous treatment with radical surgery or radiotherapy were also included. The group consisted of 1,917 patients, of whom 52% had metastatic disease, 20% had node positive or node indeterminate nonmetastatic disease and 28% had node negative, high risk nonmetastatic disease. Patients were randomized to receive ADT alone or a combination of ADT plus abiraterone 1,000 mg plus prednisolone 5 mg. This trial also mandated radiotherapy in patients with node negative nonmetastatic disease and provided the option of radiotherapy for patients with node positive nonmetastatic disease. Treatment continued until PSA, radiological or clinical

progression. In patients in whom radiotherapy was planned treatment was administered for 2 years or until any type of progression, whichever came first. Results demonstrated improved overall survival at 3 years in the combination therapy group with a 37% reduction in the relative risk compared to ADT (death HR 0.63, 95% CI 0.52–0.76, p <0.001). Failure-free survival showed a 71% relative risk reduction (treatment failure HR 0.29, 95% CI 0.25–0.34, p <0.001).

In the multicenter, phase III LATITUDE trial 1,199 patients with newly diagnosed mHSPC were enrolled within 3 months of diagnosis and randomized to receive a combination of ADT plus abiraterone 1,000 mg plus prednisolone 5 mg or ADT alone plus placebo.[20] The trial was done at a total of 235 sites in 34 countries in Europe, the Asia-Pacific region, Latin America and Canada. Patients needed at least 2 of 3 high risk features, including Gleason score 8 or greater, visceral metastasis and 3 or more bone lesions on imaging. At 3 years two-thirds of the patients in the combination group survived compared to only half of those in the placebo (ADT) group with a relative risk reduction of 38% (HR 0.62, 95% CI 0.51–0.76, p <0.001). The risk reduction was similar to that in STAMPEDE at the end of 3 years of followup (38% vs 37%).[9] Radiographic progression-free survival was improved in the combination treatment group with a 53% risk reduction (HR 0.47, 95% CI 0.39–0.55, p <0.001).

Abiraterone was well tolerated with adverse events primarily related to elevated mineralocorticoids. Grade 3 hypertension was reported in 20% of patients in LATITUDE compared to 10% on placebo. Hypokalemia was also higher in the abiraterone arm, requiring treatment discontinuation in 2 patients. STAMPEDE reported grade 3 or greater events in 15% of the combined therapy arm compared to 11% in the ADT arm.[9] Hypertension, elevated transaminases and respiratory events were reported more often in the combination therapy arm. Both studies mentioned that these side effects were medically manageable and seldom caused life threatening adverse events.

Combination therapy with abiraterone is based on the hypothesis that incomplete blockade of androgen production by ADT leads to tumor cell adaptation. By blocking CYP17 almost total suppression of extragonadal androgen production, especially from within the tumor cell, contributes to improved tumor clearance when used synergistically with ADT.[21] Median time to start abiraterone was 8 weeks after initiating ADT in the STAMPEDE trial and at the same time in the LATITUDE trial. Thus, synchronous targeting with combination therapy does not appear to alter outcomes, unlike chemohormonal therapy, which requires sequential targeting. In this context the accessory sources of androgen production are blocked, leading to almost total androgen suppression, in contrast to chemohormonal therapy, in which the hormone resistant population is targeted.

Mechanisms of Cellular Persistence after Androgen Deprivation Therapy

Two distinct and not mutually exclusive mechanisms have been proposed in the transition from hormone sensitive cells to CRPC. Tumor cells may acquire new alterations which enable them to survive in the castrated state (adaptation) or preexisting cells capable of surviving hormonal therapy may be selected after a course of ADT (selection).[22] Increased levels of intratumor androgens due to incomplete blockade by ADT, amplification of the AR gene, splice variations and a gain of function mutations, changes in the expression of coregulatory molecules to stimulate transcription after antiandrogen binding and bypass of the AR signaling pathway are examples of adaptive mechanisms.[23,24] The selection model is based on the hypothesis that clones of cells with inherent resistance to ADT are selected after ADT application. Therefore, a heterogeneous population of androgen dependent and androgen independent cells exists before ADT initiation.[25] The finding of quiescent stem cells[26] and AR deficient neuroendocrine cells, which are inherently resistant to ADT, supports this hypothesis.[27] In this context chemohormonal therapy targets selection mechanisms and abiraterone targets adaptive mechanisms.

ADT causes cellular changes in prostate cancer tissue. Apoptosis, autophagy, necrosis and necroptosis are the cell death mechanisms activated after initiating ADT.[28]

Senescence is a less studied adaptive mechanism in androgen sensitive cells.[29] Replicative senescence was first described as a phenotype in primary cells after extensive culture and replicative exhaustion in vitro that was linked to telomere shortening.[30] Induced or accelerated senescence in cancer cells results from DNA damage, increased oncogenic signaling and oxidative stress. Senescent cells remain viable and metabolically active, in contrast to apoptosis or autophagy, in which growth is arrested.[31] Markers of cellular senescence include senescence associated GLB1 (β-galactosidase) expression. Tissues from patients who underwent neoadjuvant ADT before radical prostatectomy demonstrated viable cells that frequently expressed GLB1 and accumulated after ADT.[32] Although senescence is cytostatic, cells express a SASP (secretory associated senescent phenotype). The resulting proinflammatory cytokines and growth factors may have permissive effects on surrounding

cancer cells. The unique metabolic phenotype expressed by these persistent senescent cells is characterized by a high metabolic rate, increased glycolysis, high rates of protein synthesis and down-regulation of the AMPK (5' adenosine monophosphate activated protein kinase) pathway.[33] A strategy to remove these persistent senescent cells may maximize responses to ADT and improve long-term patient outcomes.

Given the unique phenotype of these residual cancer cells, it is interesting to speculate that other less toxic agents that alter metabolism might impact ADT outcomes. One agent is the well-known oral glyburide drug metformin. Metformin directly acts on tumor cells by inhibiting the respiratory mitochondrial electron transport chain inhibiting gluconeogenesis and decreasing glucose uptake, as well as activating AMPK.[34] It also inhibits fatty acid synthesis, lipid peroxidation and the Krebs cycle, which are crucial for PC cell survival.[35] Metformin represses AR mediated signaling in hormone sensitive cell lines[36] and enhances the antiproliferative and apoptotic effect of the antiandrogen bicalutamide.[37] A putative role for metformin acting synergistically with chemotherapy has been noted in therapy resistant stem cells in breast and pancreatic tumors.[38] Interest has also arisen in examining concurrent use of statins and ADT, given inhibition of the HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme A) enzyme at the rate limiting step in the mevalonate pathway of cholesterol synthesis and the potential importance in cancer.[2] Previous combination trials using celecoxib and zoledronic acid combined with ADT in patients starting long-term hormonal therapy did not show a survival advantage.[9,39]

In a recently published retrospective study of more than 87,000 patients who were placed on ADT for advancing PC, metformin improved overall and cancer specific survival, and reduced skeletal metastases compared to diabetic men on insulin or nondiabetic men.[40] These data suggest that combining metformin with ADT could synergistically eliminate persistent cancer cells after ADT and delay the onset of CRPC. This approach ultimately requires a prospective trial. STAMPEDE is currently evaluating the combination of metformin and ADT (arm K) against the standard of care ADT (arm A) and this ongoing analysis is expected to shed light on this synergistic approach.[41]

Patient Selection for Combination Therapy of Metastatic Hormone Sensitive Prostate Cancer

Combined therapy now represents a standard of care in men with mHSPC.

ADT plus docetaxel can be offered to patients with mHSPC who are eligible for chemotherapy, particularly those with a high metastatic burden or a rapid pace of disease (fig. 2).[8] Barriers to docetaxel use include advanced patient age, poor performance status, coexisting illness and patient preference. Hematological side effects, neuropathy and fatigue are more common for chemohormonal therapy than for ADT and chemotherapy related deaths, although rare at 1% to 3%, were documented in all 3 randomized trials in which docetaxel was added. The CHAARTED and STAMPEDE docetaxel phase III trials used an 18-week course of therapy (6 cycles, each consisting of 3 weeks), and 26% and 23% of patients, respectively, in the chemohormonal therapy arm did not complete the full course of therapy. This becomes even more important in community practice, where patients with mHSPC are commonly older than those enrolled in the CHAARTED and STAMPEDE clinical trials.[42]

Abiraterone has a better side effect profile than docetaxel and, being an oral agent, it is easier to administer in the urologist office. Of patients 12% discontinued therapy due to toxic effects. In LATITUDE 88% of patients completed therapy without a dose modification.[20] In the abiraterone arm of STAMPEDE only a few patients discontinued therapy due to toxicity.[19] In LATITUDE 63% of patients reported grade 3 or 4 adverse events in the abiraterone group compared to 48% in the placebo group.[20] In STAMPEDE 47% of patients in the combination group reported grade 3 or greater adverse events compared to 33% in the placebo group.[19] Most of the latter adverse events were related to mineralocorticoid side effects, including hypertension, fluid retention and hypokalemia. Altered liver transaminases also occur more frequently with abiraterone and must be monitored. A meta-analysis of these trials revealed a threefold increase in grade 3 or greater cardiac and hepatic events, and a twofold increase in grade 3 or greater vascular events in the abiraterone combination group.[43]

Quality of life and side effects are important to consider in most men who were otherwise asymptomatic. In patients with low volume disease or significant comorbid conditions ADT alone remains an appropriate treatment option, which should be discussed in individualized counseling. The duration of treatment with abiraterone is longer at 2 years or more. This raises concerns about safety, especially in patients with preexisting risk factors for cardiovascular disorders and stroke. STAMPEDE excluded men with a significant cardiac history, limiting generalizations of benefit or toxicity in those patients. A short course of docetaxel might be preferred in patients with good performance status to avoid the long-term effects of steroids and the toxicity associated with abiraterone, including hyperglycemia, cardiovascular risks, osteopenia

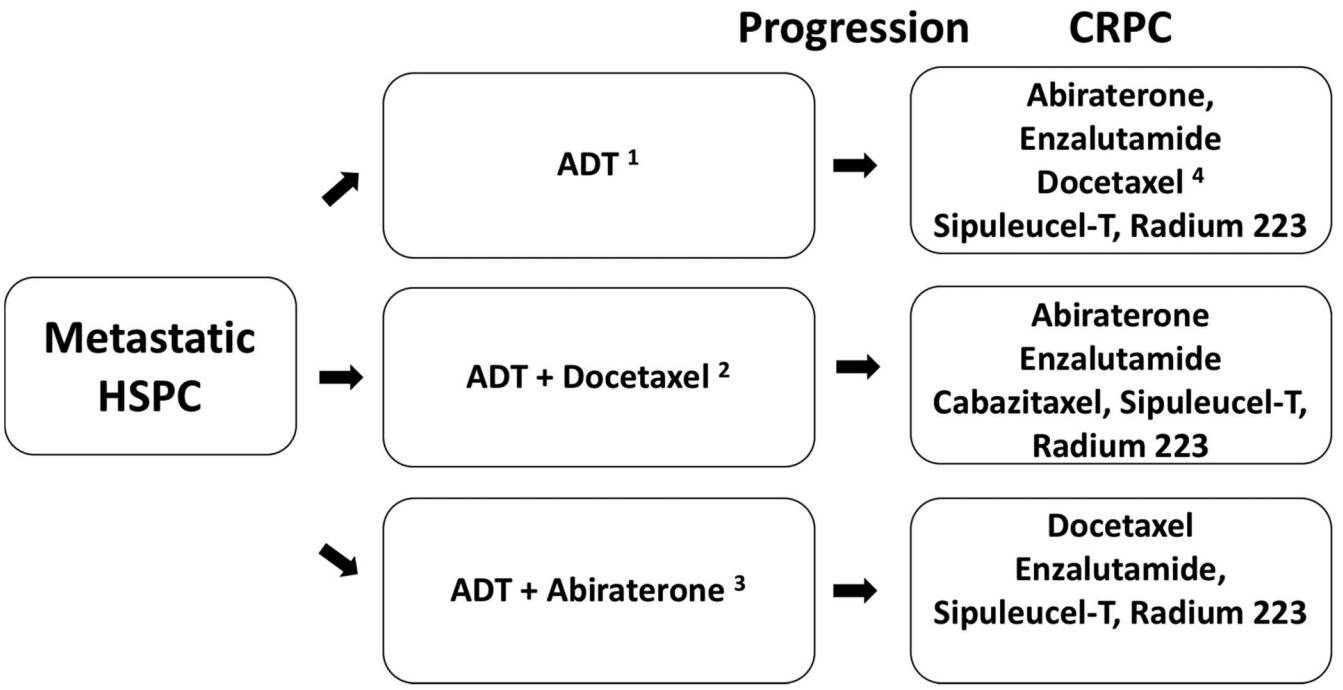

Figure 2. Optimizing treatment of newly diagnosed mHSPC. *1*, patients with poor performance status or desire to avoid therapy side effects may elect ADT alone. *2*, CHAARTED showed 37% relative risk reduction in high volume metastatic subgroup (more than 4 metastases) compared to 27% overall. *3*, LATITUDE included patients with de novo metastatic disease and 2 of 3 high risk features, namely Gleason score 8 or greater, visceral metastasis and 3 or more bone lesions on imaging. *4*, treatment depends on life expectancy and performance status.

and/or osteoporosis. The requirement for concurrent prednisone with abiraterone can limit its use in patients with brittle diabetes, patients with chronic gastric ulcers and patients with infection.

This raises the question of the ideal therapeutic agent in the setting of mHSPC. To our knowledge a direct head-to-head comparison of ADT plus abiraterone or docetaxel has not been performed, limiting conclusions. A recent analysis of STAMPEDE indicated that contemporaneously randomized patients showed no evidence of a difference in overall or PC specific survival, or in symptomatic skeletal events.[44] Interestingly, failure-free survival favored abiraterone, likely reflecting the PSA response and the mechanism of action. The docetaxel cohort had more durable survival after failure. Toxicity was similar between the arms with an 11% prevalence of grade 3 or 4 toxicity at 1 year. The question has been raised whether a combination of abiraterone plus docetaxel (and ADT) might lead to an additive benefit in survival. Data on this will emerge from the ongoing PEACE1 (Phase III Study for Patients with Metastatic Hormone-naïve Prostate Cancer) trial.

The cost of long-term abiraterone treatment is also a factor that physicians and patients should consider before starting therapy. While the cost of docetaxel for a 6-cycle course is estimated to be about $20,000, the cost of abiraterone for a 2-year course can exceed $120,000 per patient.[45,46] While cost analyses have been completed for abiraterone in men with CRPC, to our knowledge they have not been reported in the HSPC setting. Given the extended treatment duration of abiraterone in HSPC cases, often exceeding 2 years, the potential costs can be significant. The fluid nature of prescription drug coverage across different insurers, especially for oral agents, has made it difficult to predict year-to-year costs of these agents. This represents a new world for many prescribers in which monitoring patient costs for these agents is a critical issue requiring close collaboration with oncology pharmacists. The emergence of new assistance programs for these expensive therapies requires dedicated staff to guide patients through these applications.

Ongoing and Future Trials

Recent positive phase III trials have led to a wealth of new trials in the mHSPC space. Combining ADT with the androgen axis inhibitors enzalutamide, apalutamide and orteronel are ongoing (table 2). Enzalutamide is an androgen signaling inhibitor with multiple actions, including blocking AR translocation to the nucleus, AR binding to DNA and receptor mediated DNA transcription.[47] It has been approved in men with advancing CRPC before and after docetaxel chemotherapy, and recently for

Table 2. *Ongoing phase III trials of combination therapy with ADT in metastatic hormone sensitive prostate cancer*

Trial Type/Name	ClinicalTrials.gov Identifier	Phase/No. Enrolled	Intervention	Primary End Point	Estimated Completion
Hormonal:					
ENZAMET	NCT02446405	III/1,125	ADT + enzalutamide vs ADT + nonsteroidal anti-inflammatory drug	Overall survival	9/2020
ARCHES	NCT02677896	III/1,100	ADT + enzalutamide vs ADT + placebo	Radiographic progression-free survival	4/2020
STAMPEDE	NCT00268476	II/III/—	ADT vs ADT + abiraterone + enzalutamide (Arm J)	Overall survival	2020
TITAN	NCT02489318	III/1,000	ADT + apalutamide vs ADT + placebo	Overall + radiographic progression-free survival	11/2020
SWOG S1216	NCT01809691	III/1,304	ADT + orteronel vs ADT + bicalutamide	Overall survival	3/2022
Metabolic (STAMPEDE)	NCT00268476	II/III/—	ADT vs ADT + metformin (Arm K)	Overall survival	2020
Chemotherapy (PEACE1)	NCT01957436	III/1,168	ADT +/− docetaxel +/− abiraterone +/− radiation	Overall + radiographic progression-free survival	5/2019

nonmetastatic CRPC with rapidly rising PSA, as shown in PROSPER (Safety and Efficacy Study of Enzalutamide in Patients With Nonmetastatic Castration-Resistant Prostate Cancer). It is being evaluated as combination therapy with ADT for mHSPC separately as well as an adjunct with another androgen axis inhibitor, abiraterone. Apalutamide, which is similar to enzalutamide in action, was recently approved for nonmetastatic CRPC with rapidly rising PSA while on ADT (SPARTAN, Study of Apalutamide [ARN-509] in Men With Non-Metastatic Castration-Resistant Prostate Cancer).[48] Orteronel is a selective nonsteroidal inhibitor of 17,20 lyase, a key enzyme in androgen synthesis. It has shown significant activity in the setting of CRPC.[49] Combination therapy with these additional androgen axis inhibitors is expected to contribute to the evolving landscape of mHSPC management.

The synergistic combination of chemotherapy with androgen axis inhibition was also evaluated in combination with radiation therapy (table 2). Metformin is also being assessed in combination with ADT in arm K of STAMPEDE. The side effect profile and low cost would make this an attractive adjunct in the management of prostate cancer if the results show a synergistic benefit. Finally, ADT induces an AR specific T-cell response, suggesting that ADT combined with AR directed immunotherapy might be an alternate approach to prevent the development of AR over expressing CRPC clones.[50] This approach represents an intriguing and potentially less toxic strategy for future trials.

CONCLUSIONS

It is remarkable that for more than half a century after its introduction androgen suppression remained the preferred front line approach to the treatment of hormonally sensitive, metastatic prostate cancer. With the development of cytotoxic regimens with clinically relevant activity in CRPC earlier combination trials in men with mHSPC have demonstrated significant improvements in survival and QOL. ADT and docetaxel or abiraterone should be considered the standard of care in these patients.

ADT induces adaptive changes in PC cells and selects resistant clones, leading to castration resistance. The susceptibilities generated by ADT can be synergistically targeted to improve survival outcomes and delay the onset of CRPC, as shown in several recent combination trials. Novel approaches targeting metabolic pathways have the potential to be synthetically lethal with ADT by targeting the multiple susceptibilities induced by ADT. This area needs to be explored in further clinical trials.

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