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Treatment of Metastatic Prostate Cancer in 2018

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Treatment of advanced and metastatic prostate cancer has rapidly evolved with the approval of multiple agents, which improve overall survival (OS) in patients with metastatic castration-resistant prostate cancer (CRPC). In addition, there is growing evidence that use of these agents earlier in the disease course provides clinical benefit and an OS advantage. Herein, we review the shift toward earlier use of agents in the course of advanced prostate cancer.

In 2018, androgen deprivation therapy (ADT) remains the backbone of systemic therapy for prostate cancer. Use of docetaxel and abiraterone acetate were originally limited to patients with metastatic CRPC, but recently these agents have been studied in both lower- and higher-risk populations with progression of disease while not receiving ADT, or so-called hormone sensitive prostate cancer (HSPC). The use of 6 cycles of docetaxel, 75 mg/m², in HSPC is supported by two phase 3 clinical trials (CHAARTED¹ and STAMPEDE²). In both studies, early initiation of docetaxel in conjunction with ADT in patients with metastatic HSPC was associated with improved OS compared with ADT alone (CHAARTED: 576 vs 47.2 months; hazard ratio [HR], 0.72; 95% CI, 0.59-0.89; $P = .002$; STAMPEDE: 60 vs 45 months; HR, 0.76; 95% CI, 0.62-0.92; $P = .005$). Overall, this regimen is well tolerated. However, the role of docetaxel in patients with low-volume metastatic and nonmetastatic disease is less clear. In a subgroup analysis of CHAARTED, early docetaxel treatment was associated with improved OS (51.2 vs 34.4 months; HR, 0.63; 95% CI, 0.50-0.79; $P < .001$) in patients with high-volume disease (presence of visceral metastases or ≥ 4 bone lesions, with ≥ 1 beyond the vertebral body or pelvis), whereas in patients with low-volume disease, no improvement in OS was seen (63.5 vs not reached; HR, 1.04; 95% CI, 0.70-1.55; $P = .86$). These data are further supported by results from GETUG-AFU 15,³ a study of largely good-risk patients (ie, $>50\%$ of patients with low-volume disease), which also did not show an improvement in OS (not reached vs 83.4 months; HR, 1.02; 95% CI, 0.67-1.55; $P = .90$). Together, these data suggest that docetaxel should be considered for patients with more aggressive (de novo [those who initially present with metastatic disease] and/or high-volume metastatic) HSPC.

The combination of abiraterone acetate and prednisone in addition to ADT has been tested for HSPC in 2 randomized phase 3 trials, LATITUDE⁴ and STAMPEDE.⁵ In LATITUDE, initiation of abiraterone acetate in patients with high-risk disease was associated with improved OS compared with ADT alone (not reached vs 34.7 months; HR, 0.62; 95% CI, 0.51-0.76; $P < .001$). High-risk disease was defined as having at least 2 risk factors (Gleason score of ≥ 8 , ≥ 3 bone metastases, visceral disease). These results were further supported by findings from the STAMPEDE trial, which included patients with N1 or high-risk N0M0 disease in addition to patients with metastatic disease. In this heterogeneous mix of patients, abiraterone acetate in combination with ADT showed an improvement in OS in the overall trial population (HR, 0.63; 95% CI, 0.52-0.76; $P < .001$). These data support early initiation of abiraterone acetate for high-risk patients. A direct comparison of the addition of abiraterone acetate or docetaxel to ADT showed no differences in OS and similar rates of grade 3,4, or 5 adverse events; however, adverse effect profiles of abiraterone acetate and docetaxel were different but consistent with known adverse effects of the regimens.⁶ However, this study may have been underpowered to show small differences between the regimens. Currently, the choice between early initiation of docetaxel or abiraterone acetate should be made on an individual basis considering the patient's prognosis and comorbidities (Figure). Sydes et al⁶ generally favor the use of abiraterone acetate plus prednisone in combination with ADT because of ease of administration. The exception would be patients with high-volume or de novo metastatic HSPC wherein the benefits of docetaxel are seen, leaving abiraterone acetate for consideration at a later point in treatment.

In patients with nonmetastatic CRPC, additional options are now available. In the nonmetastatic CRPC, apalutamide and enzalutamide were tested in patients with a prostate-specific antigen doubling time of less than 10 months.^{7,8} In the SPARTAN trial,⁸ apalutamide (vs placebo) improved metastasis-free survival (40.5 vs 16.2 months; HR, 0.28; 95% CI, 0.23-0.35; $P < .001$). In the PROSPER trial,⁷ enzalutamide (vs placebo) also improved metastasis-free survival (33.6 vs 14.7 months; HR, 0.29; 95% CI, 0.24-0.35; $P < .001$). These studies led to regulatory approval of apalutamide and enzalutamide for patients with nonmetastatic CRPC. While metastasis-free survival was dramatically improved, an OS benefit has yet to be seen, so careful weighing of risks and benefits of adding these agents should be made in patients with nonmetastatic disease. Nonmetastatic CRPC denotes a state of nonradiographically evident metastatic CRPC; however, given the burden of treatment with these agents and the current lack of evidence for an OS advantage, we remain cautious about selecting appropriate patients for treatment. Optimal patients would be those with rapid prostate specific antigen doubling times and at low risk for treatment-related adverse effects. We regard these agents to be essentially equivalent in efficacy and likely toxicity, although no head-to-head comparison exists (Figure).

For patients with metastatic CRPC, sipuleucel-T, abiraterone acetate, enzalutamide, docetaxel, cabazitaxel, and radium-223 have improved clinical outcomes; however, molecular biomarkers that predict clinical responses to these agents remain elusive. For patients who have not received any of these agents for HSPC, the optimal sequencing of these agents in metastatic CRPC remains unclear. Extent and tempo of disease play a major role in the decision process. For asymptomatic or minimally symptomatic patients with low-volume disease and slower progression, sipuleucel-T can be considered. For more

symptomatic patients and/or those whose disease is progressing more rapidly, either abiraterone acetate or enzalutamide or alternatively docetaxel should be considered as a primary treatment, leaving the remaining agents to be used subsequently sequentially. Pathogenic germline mutations can be seen in up to 20% of patients.⁹ In metastatic CRPC, the prevalence of microsatellite instability-high (MSI-H) or a marker of mismatch repair deficiency is seen in approximately 2% to 5% of patients and supports broader testing in this population. Furthermore, the identification of mutations in homologous recombination repair and DNA repair pathways, such as BRCA1/2, have also been associated with improved responses to PARP (poly ADP-ribose polymerase) inhibitors such as olaparib and DNA damaging agents such as platinum chemotherapy.¹⁰ This suggests the need for both germline and somatic testing of the tumor, which is not standard in most next-generation sequencing platforms owing to concerns regarding hereditary implications.

Systemic therapy for prostate cancer has improved clinical outcomes for patients with advanced prostate cancer; however, the integration of molecular biomarkers into the treatment paradigm remains at its infancy. We are beginning to see molecular stratification change clinical management; however, further development of these biomarkers is necessary as the treatment of prostate cancer enters the era of genomics and personalized medicine.

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Figure. Suggested Treatment Paradigm for Molecular Biomarkers in Advanced Prostate Cancer
ADT indicates androgen deprivation therapy; mCRPC, metastatic castration-resistant prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer; nmCRPC, nonmetastatic castration-resistant prostate cancer; nmHSPC, nonmetastatic hormone-sensitive prostate cancer.