Management of Metastatic Prostate Cancer

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ABSTRACT

Androgen deprivation therapy is a well-established standard of care for the management of metastatic prostate cancer; however, recent studies have investigated additional therapeutic options, escalation strategies, and primary directed therapy for patients with advanced disease. Treatment decisions are based on clinical parameters, disease characteristics, and patient factors. At the NCCN 2023 Annual Conference, a panel of experts used 3 case studies to develop an evidence-based approach for the treatment of patients with metastatic prostate cancer. The session focused on the current research regarding both systemic and local therapy options in each clinical context.

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Treatment decisions for metastatic prostate cancer (PC) are often dictated by tumor location and biology and the health status of the patient, despite androgen deprivation therapy (ADT) being a well-established standard of care in this disease setting. At the NCCN 2023 Annual Conference, a panel of experts presented on current strategies for the management of metastatic PC. The session focused on 3 case studies, which were used to develop an evidence-based approach for the treatment of similar patients. Panelists included Archana Ajmera, MSN, ANP-BC, AOCNP, Oncology Nurse Practitioner, UC San Diego Moores Cancer Center; Rana R. McKay, MD, Associate Professor of Medicine and Urology, UC San Diego Moores Cancer Center, and member of the NCCN Guidelines Panel for Prostate Cancer; and Kelly L. Stratton, MD, Associate Professor of Urologic Oncology, University of Oklahoma Health Stephenson Cancer Center.

Case 1: Metastatic Hormone-Sensitive PC

The first case presentation focused on a patient with an elevated prostate-specific antigen (PSA) level who was diagnosed with a poorly differentiated adenocarcinoma with a Gleason score of 10; all 12 cores appeared to be involved. Prostate-specific membrane antigen (PSMA) PET imaging revealed innumerable pulmonary metastases, hypermetabolic mediastinal and bilateral hilar adenopathy, and multiple pelvic lymph nodes.

"The treatment landscape for metastatic hormone-sensitive PC has really evolved since 2015," Ms. Ajmera remarked. "Although ADT is still the backbone of therapy, the treatment landscape has [expanded] to include doublet and triplet therapy." Per the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for PC, there is category 1 evidence supporting the efficacy of doublet therapy with this ADT backbone + abiraterone, apalutamide, or enzalutamide, as well as triplet therapy with ADT + docetaxel and either abiraterone or darolutamide (Figure 1).[1]

Recently, a series of trials demonstrated an overall survival (OS) benefit for doublet therapy with ADT + either chemotherapy (CHAARTED, STAMPEDE) or an androgen signaling pathway inhibitor (LATITUDE, STAMPEDE, TITAN, ARCHES, ENZAMET) in the metastatic hormone-sensitive disease setting. Additionally, the CHAARTED and LATITUDE trials provided the background to further define high-volume/high-risk disease.[2] Subsequent trials of triplet therapy, such as ARASENS and PEACE-1, tested the additional of darolutamide and abiraterone, respectively, to the backbone of ADT + docetaxel (ClinicalTrials.gov identifiers: NCT02799602 and NCT01957436). These studies further investigated outcomes by volume/risk of disease.

CHAARTED demonstrated a benefit for chemotherapy in high-volume patients. LATITUDE, which only included patients with de novo high-risk disease, demonstrated a benefit for abiraterone in patients with metastatic high-risk prostate cancer.[3] Findings of the phase III ARASENS trial, however, revealed that triplet therapy with ADT + docetaxel + darolutamide was favored over doublet therapy for OS, as well as for all secondary endpoints, regardless of criteria-based volume or risk for both studies; the addition of darolutamide did not seem to significantly increase the incidence of toxicities.[4,5]

In the phase III PEACE-1 trial, ADT + docetaxel + abiraterone seemed to improve OS outcomes compared with doublet therapy, although this benefit was largely driven by patients with high-volume disease.[6] Despite the previously mentioned outcomes, it is important to note that hypertension and hepatotoxicity were reported more frequently with triplet versus doublet therapy.

"We can say that men with a higher burden of metastatic PC could potentially live longer if they receive

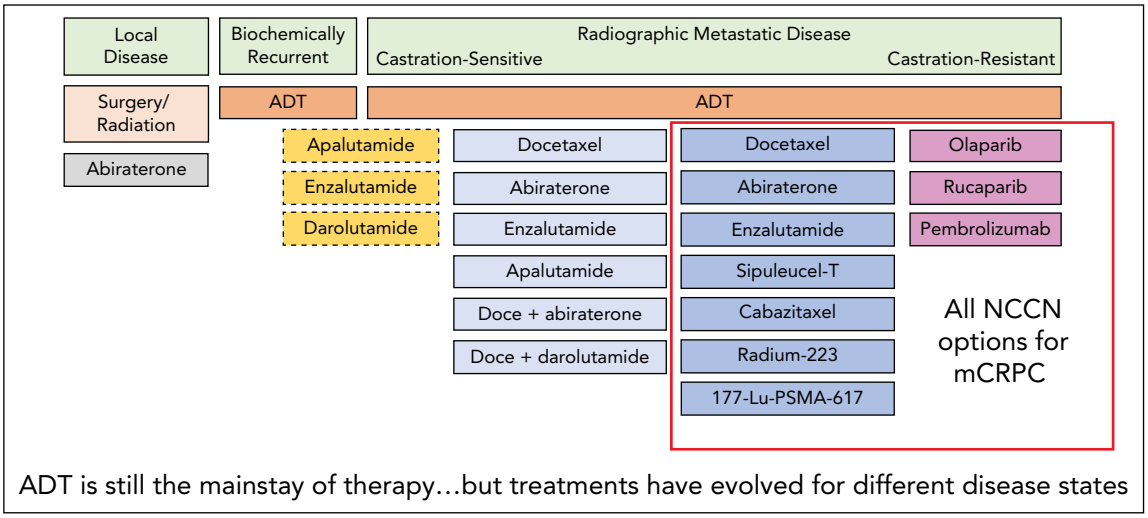

Figure 1. Treatment landscape for advanced prostate cancer.
Abbreviations: ADT, androgen deprivation therapy; Doce, docetaxel; mCRPC, metastatic castration-resistant prostate cancer.
Data from NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Prostate Cancer, Version 1.2023. To view the most recent and complete version of these guidelines, visit www.nccn.org.

3 agents," Ms. Ajmera commented. "This was really practice-changing. Keep in mind that the control in these studies was ADT + docetaxel so we do not know how ADT androgen receptor signaling inhibitors [ARSIs] would fare in this setting."

In addition to volume and risk, the timing of metastasis is a disease factor that has been found to influence survival outcomes. A subgroup of patients from the CHAARTED trial with recurrent low-volume disease seemed to experience a prolonged median duration of OS compared with those with de novo high-volume disease.[7] Furthermore, metachronous versus de novo metastases matter with metachronous associated with better outcomes compared with de novo metastases.

Clinical factors to consider in administration of these regimens include symptoms, performance status, whether the patient may tolerate chemotherapy, comorbidities, and concurrent medications (Figure 2). In terms of drug factors, financial toxicities play a vital role in determining whether to select a particular therapy. Docetaxel has a finite number of doses, is administered once every 3 weeks, and potentially has less financial toxicity for the patient. Oral agents, such as abiraterone, apalutamide, enzalutamide, and darolutamide, are administered daily until disease progression and tend to be more costly.

The patient in this case received ADT with the oral gonadotropin-releasing hormone antagonist relugolix followed by abiraterone and prednisone. As a result of this regimen, his PSA level declined, and he achieved an undetectable PSA level after treatment with docetaxel. A follow-up PSMA PET scan revealed a partial response.

Case 2: Metastatic Castration-Resistant PC

The second case focused on an 80-year-old male diagnosed with high-risk, Gleason score 8 disease that appeared to be confined to the prostate. He was initially

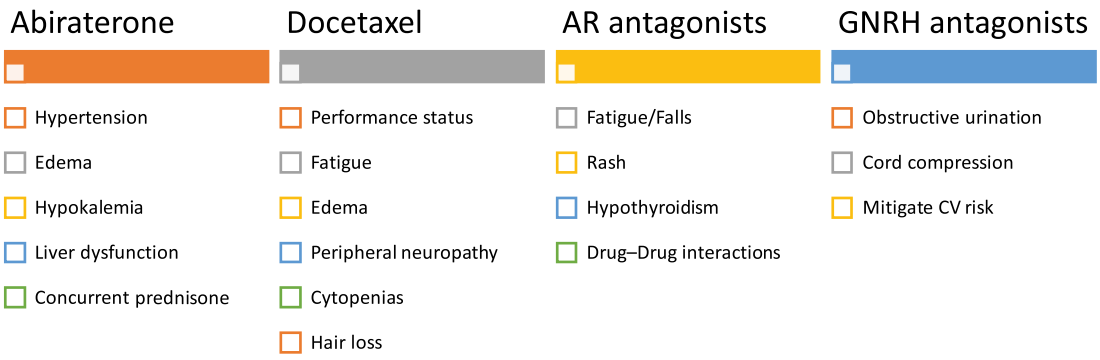

Figure 2. Clinical factors to consider in administration of treatment regimens.
Abbreviations: AR, androgen receptor; CV, cardiovascular; GNRH, gonadotropin-releasing hormone.

treated with radical prostatectomy and unfortunately developed recurrent disease and was treated with salvage external-beam radiation therapy (EBRT) + ADT. He subsequently experienced recurrence and was treated with intermittent ADT and ultimately developed metastatic castration-resistant PC (CRPC). He was initially treated with abiraterone, which resulted in PSA stabilization and ultimately radiographic progression, and then docetaxel, which resulted in initial PSA stabilization followed by radiographic progression after 6 cycles of treatment. The patient underwent germline and somatic tumor profiling with both tissue and circulating tumor DNA testing. "[The results highlight] the evolution of advanced PC and the need to continue to check these patients for acquired alterations," commented Dr. McKay.

Dr. McKay then discussed the current treatment landscape of this disease, with a particular focus on ^{177}Lu-PSMA-617. This radioligand therapy has been granted a category 1 recommendation for use in certain circumstances, and it was ultimately deemed the appropriate treatment for Case 2 (Figure 1).[1]

The phase III VISION trial was conducted to evaluate the safety and efficacy of ^{177}Lu-PSMA-617 in patients with PSMA-positive disease who previously received treatment with both an ARSI and taxane-based chemotherapy regimen. Patients were randomly assigned to receive standard-of-care therapy ± ^{177}Lu-PSMA-617. The primary analysis demonstrated improved OS and radiographic progression-free survival outcomes in all patients with the addition of radioligand therapy.[8] Furthermore, according to Dr. McKay, the addition of ^{177}Lu-PSMA-617 improved both the objective response rate and PSA responses. "I think [one of] the biggest things to watch out for with this regimen are fatigue and myelosuppression," she remarked. Dry mouth, nausea and vomiting, and renal effects were also among the most frequently reported adverse events.

In 2022, the FDA approved ^{177}Lu-PSMA-617 for the treatment of adults with PSMA-positive metastatic CRPC who had previously received an ARSI and taxane-based chemotherapy.[9]

Case 2 was treated with ^{177}Lu-PSMA-617 plus the ARSI enzalutamide. His PSA level declined after 4 cycles of therapy; PSMA PET imaging further highlighted the clinical benefits conferred by this combination. "We saw a dramatic decline in his PSA, more so than with any of the other prior regimens he had been on," Dr. McKay commented.

Dr. McKay discussed other clinical trials that have explored systemic therapy regimens in the metastatic CRPC; particularly, she focused on those evaluating the efficacy of sequential androgen receptor signaling inhibition. "Several studies, including CARD[10] and the control arm of PROfound,[11] have demonstrated inferior outcomes with sequential androgen receptor–targeted agents compared with switching to an agent with an alternate mechanism of action," she remarked.

In the CARD trial, patients previously treated with docetaxel and who had experienced disease progression within 12 months of treatment with an ARSI were randomly assigned to receive either cabazitaxel + prednisone and a granulocyte colony-stimulating factor or an alternate ARSI. Compared with the latter, switching therapy to cabazitaxel was found to improve imaging-based radiographic progression-free survival (3.7 vs 8.0 months) and OS (11.0 vs 13.6 months) outcomes in this population.[10]

The PROfound trial enrolled patients with *BRCA1/2* or *ATM* mutations (cohort A) or other homologous recombination repair alterations (cohort B) who previously underwent androgen receptor signaling inhibition. Within these biomarker-selected cohorts, patients were randomly assigned to receive either olaparib (300 mg) or the physician's choice of ARSI therapy. Cohort A seemed to derive a significant OS benefit with olaparib (14.1 vs 11.5 months).[11] In cohort B, OS was numerically but not significantly different between the arms; however, according to Dr. McKay, the degree of benefit was variable depending on the specific genetic alteration.

Case 3: Local Treatment of Metastatic Disease

Dr. Stratton reviewed the local treatment landscape for metastatic PC prior to presenting the third patient profile. He offered a few reasons why the primary tumor should be treated: prevention of additional metastases from the primary tumor; induction of an immunogenic response to release tumor antigens; and disruption of signaling from the primary tumor to metastatic foci. Preclinical studies suggested this approach may be beneficial, which prompted initiation of the STAMPEDE trial.

In the multicohort STAMPEDE trial, patients with newly diagnosed metastatic PC were randomly assigned to receive standard-of-care ADT alone or in combination with a variety of interventions; the standard of care was amended to include docetaxel in 2015.[12] Of particular relevance, patients in cohort H were administered the standard of care + local RT.[13] This regimen did not appear to improve OS outcomes in all-comers; however, a failure-free survival benefit was reported, and the regimen was found to be well tolerated.[12] However, the benefit of primary radiation therapy was observed in patients with low-volume disease.

"[The investigators hypothesized] that patients with low metastatic burden were probably going to be the most likely to benefit from local treatment," explained Dr. Stratton. "When we look at that prespecified subgroup analysis of low-volume versus high-volume disease, that is where we see that their hypothesis was, in fact, correct." Patients with CHAARTED-defined low-volume metastatic disease were

found to experience improved OS and failure-free survival outcomes, whereas those with high-volume disease did not seem to derive the same benefit.[12]

Based on a secondary analysis, local RT was found to significantly improve OS (hazard ratio, 0.62; 95% CI, 0.46–0.83) and failure-free survival (hazard ratio, 0.57; 95% CI, 0.47–0.70) outcomes in patients with low metastatic burden who had either nonregional lymph node disease or ≤3 bone metastases without visceral disease; this did not seem to hold true in those with high-volume disease.[14] According to Dr. Stratton, these findings are reflected in the NCCN Guidelines for the treatment of patients with castration-sensitive PC.[1]

In the third case presentation, a 50-year-old patient presented with an elevated PSA level, although a digital rectal examination did not detect any irregularities. Continuing to follow the procedure outlined in the NCCN Guidelines for PC Early Detection, Dr. Stratton opted to conduct a multiparametric MRI, which showed a PI-RADS 4 lesion. After undergoing a transperineal fusion biopsy, the patient was diagnosed with high-risk, Gleason score 8 disease. Conventional imaging revealed 2 metastatic lesions in the thoracic spine and 1 in the sacrum.

"Nowadays, we can consider using a PSMA PET scan," Dr. Stratton remarked. "I still think there is utility in obtaining conventional imaging for patients who are undergoing metastatic evaluation."

Based on findings from the secondary analysis of the STAMPEDE trial, the NCCN Guidelines recommend ADT + EBRT to the primary tumor for patients with castration-sensitive PC and low metastatic burden.[1,14] Luteinizing hormone-releasing hormone (LHRH) agonists, LHRH antagonists, and orchiectomy are the suggested ADT options in this clinical context. Additionally, per the NCCN Guidelines, Dr. Stratton noted that "We see, from a couple of different perspectives, the consideration for combining ADT in patients receiving RT for low metastatic burden PC."

In the present case, the patient underwent ADT in combination with leuprolide and local RT. He subsequently achieved an undetectable PSA level, which continues to be maintained to this day.

*These authors have contributed equally.

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