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Expert Perspectives on Controversies in Metastatic Castration-Resistant Prostate Cancer Management: Narrative Review and Report of the First US Prostate Cancer Conference Part 2

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Abstract

Background: Management strategies for metastatic castration-resistant prostate cancer (mCRPC) have rapidly shifted in recent years. As novel imaging and therapeutic approaches have made their way to the clinic, providers are encountering increasingly challenging clinical scenarios, with limited guidance from the current literature.

Materials and Methods: The US Prostate Cancer Conference (USPCC) is a multidisciplinary meeting of prostate cancer experts intended to address the many challenges of prostate cancer management. At the first annual USPCC meeting, areas of controversy and consensus were identified during a 2-day meeting that included expert presentations, full-panel discussions, and postdiscussion responses to questions developed by the USPCC cochairs and session moderators.

Results: This narrative review covers the USPCC expert discussion and perspectives relevant to mCRPC, including neuroendocrine/aggressive-variant prostate cancer (NEPC/AVPC). Areas of broad agreement identified among USPCC experts include the benefits of poly (ADP-ribose) polymerase (PARP) inhibitors for patients with *BRCA1/2* mutations, the use of radioligand therapy in patients with prostate-specific membrane antigen (PSMA)–positive mCRPC, and the need for clinical trials that address real-world clinical questions, including the performance of novel therapies when compared with modern standard-of-care treatment. Ongoing areas of controversy and uncertainty included the appropriateness of PARP inhibitors in patients with non-*BRCA1/2* mutations, the optimal definition of PSMA positivity, and systemic therapies for patients with NEPC/AVPC after progression on platinum-based therapies.

Conclusions: The first annual USPCC meeting identified several areas of controversy in the management of mCRPC, highlighting the urgent need for clinical trials designed to facilitate treatment selection and sequencing in this heterogeneous disease state.

Keywords

prostatic neoplasms; androgen antagonists; radiotherapy; biomarkers; precision medicine

OVER the past decade, treatment options for metastatic castration-resistant prostate cancer (mCRPC) have expanded rapidly.[1] With the recent addition of so many novel agents, combinations, and drug classes, clinicians are faced with increasingly complex decision-making processes related to the selection and sequencing of systemic therapies. These decisions are further complicated by the availability and integration of molecular targeted imaging and theranostics into clinical practice. Across these new management strategies, level 1 clinical trial evidence is lacking, presenting a challenge for clinicians who manage mCRPC.

In contrast with the bevy of options for castration-resistant prostatic adenocarcinoma, few treatment options are available for less common variants of the disease, such as neuroendocrine prostate cancer (NEPC). The diagnosis of NEPC is currently based on pathologic features showing poorly differentiated neuroendocrine features (typically small-cell carcinoma). In the absence of metastatic biopsy, clinical features of aggressive disease (ie, aggressive-variant prostate cancer [AVPC]) can also be used to identify patients who may benefit from treatment intensification. Both NEPC and AVPC are associated with androgen receptor (AR)–independent features, including loss of expression of luminal prostate and AR signaling markers and simultaneous *RB1*, *PTEN*, and *TP53* tumor suppressor loss. While de novo NEPC/AVPC is considered rare, more recent studies suggest that NEPC/AVPC may be an underrecognized transformation in patients with mCRPC who progress on treatment.[2] Given the poor prognosis of NEPC and AVPC, standardized approaches to disease identification, monitoring, and treatment are needed to better align with the dynamic morphologic and genomic changes characteristic of NEPC/AVPC transformation.

To address these and other conundrums of advanced prostate cancer (PCa) management, a multidisciplinary panel of PCa experts was convened in 2023, with the goal of identifying areas of consensus and controversy across the spectrum of PCa. At the first annual US Prostate Cancer Conference (USPCC), the topics and discussion were intentionally focused on areas of complexity in the management of PCa. In this manuscript, the second in a 2-part USPCC series, discussions and outcomes related to late-stage PCa—specifically mCRPC and NEPC/AVPC—are reported.

MATERIALS AND METHODS

As described in part 1,[3] the USPCC was held on February 18 and 19, 2023, and consisted of 9 sessions on the topics of androgen deprivation therapy (ADT), high-risk PCa, biochemical recurrence, metastatic castration-sensitive PCa, metastasis-directed therapy, NEPC/AVPC, mCRPC, poly(ADP-ribose) polymerase inhibitors (PARPis), and theranostics. These topics were selected collaboratively by USPCC co-chairs and were moderated by USPCC panel members considered experts in each subject. These moderators were responsible for identifying clinical challenges and unanswered questions within the subject area, designing

the discussion agenda, and developing discrete-choice questions discussed qualitatively in this report. Each meeting session included prepared expert presentations, moderated discussions among all USPCC contributors, and anonymous voting. Although voting was encouraged, it was not required that panel members answer all questions. Questions and responses for the sessions on mCRPC, PARPis, theranostics, and NEPC/AVPC can be found in Supplemental Appendix 1 (http://links.lww.com/JU9/A65).

The results of the USPCC discussions on mCRPC and NEPC/AVPC are reported here.

RESULTS AND DISCUSSION

mCRPC

Guidance for the selection and sequencing of systemic therapy for mCRPC is limited. Current National Comprehensive Cancer Network (NCCN) guidelines stratify treatment recommendations based on receipt of prior docetaxel and/or prior AR pathway inhibitor (ARPi).[4] Additional guidance regarding selection of agents across and within drug classes, however, is lacking. This is particularly true for the newest treatment options, including PARPi monotherapy, PARPi combination therapy, and radioligand therapy (RLT). Furthermore, biomarker-driven patient selection in PCa is still in its infancy, and clinical trials are needed to determine which patients will benefit most from newly approved targeted treatment approaches. As such, USPCC discussions about mCRPC centered on appropriate PARPi use, theranostics and RLT, and unmet needs in mCRPC treatment, including investigational therapies and future research priorities.

Homologous Recombination Repair Testing and PARPis.—Between 20% and 25% of patients with advanced PCa have homologous recombination repair (HRR) gene mutations,[5–7] indicating a potential role for targeted therapy in up to 1 in 5 men with mCRPC. And yet, clinical uptake of genomic testing in patients with PCa is highly heterogeneous in the United States, with studies showing that most men with mCRPC do not receive HRR genetic testing.[8–11] To address this deficiency, USPCC experts emphasized the need for standardization of somatic tumor testing for HRR mutations in all patients with mCRPC, regardless of prior genetic testing results. Indeed, 81% of USPCC experts indicated that they would recommend repeat genetic testing after development of mCRPC in a patient whose primary tumor was negative for HRR gene mutations. Although metastatic tissue biopsy is the preferred method for molecular evaluation among USPCC experts and guidelines, 59% of USPCC experts indicated that circulating tumor DNA (ctDNA) testing could be used without tissue testing. This recommendation is aligned with NCCN guidelines, which indicate that ctDNA testing may be used when biopsy is not feasible. Importantly, USPCC experts emphasized that serum levels of ctDNA can be dependent on tumor volume, and samples should ideally be collected during radiographic progression to maximize the diagnostic yield.[4]

One major and ongoing question related to the use of PARPis is optimal patient selection, particularly for those with non-*BRCA1/2* HRR gene mutations. Among the 5 current US Food & Drug Administration (FDA) approvals for PARPis in mCRPC, 3 are restricted to tumors with deleterious aberrations in *BRCA1/2* while 2 approvals include a larger panel

of alterations. USPCC panelists noted, however, that PARPis have been associated with the greatest benefit in *BRCA2*-altered tumors, with lower response rates in non–*BRCA2*-altered disease.[12] As a result, USPCC experts were divided on whether PARPi monotherapy should be offered to patients with non-*BRCA1/2* HRR gene mutations: 38% agreed, 38% disagreed, and 16% were not sure. For the most part, USPCC members who agreed that PARPis should be offered to patients with non-*BRCA1/2* HRR gene mutations noted that PARPis would be one of many treatment options discussed as part of shared decision-making.

Another important question addressed during the USPCC meeting was the optimal duration of PARPi therapy in patients with durable responses. In the TRITON and PROfound trials, PARPis were continued until disease progression or unacceptable toxicity,[13–15] and all PARPis are approved on continuous, daily dosing schedules. Nonetheless, PARPis are associated with progressive myelosuppression and a risk of developing myelodysplastic syndrome/acute myeloid leukemia.[16] In light of these risks, just less than one-third of USPCC members indicated that they would consider a drug holiday to reduce long-term toxicity in patients with deep responses to PARPis. Overall, USPCC experts agreed that, if PARPis were to be withheld or paused for reasons other than toxicity, close follow-up is necessary to ensure prompt reinitiation of PARPi or another systemic therapy in case of disease progression.

Combination Therapy With PARPis and ARPis.—At the time of the meeting, FDA adjudication was still pending for combination therapy with both niraparib plus abiraterone and talazoparib plus enzalutamide. Nevertheless, the trial data were available, and the panel debated the appropriateness of PARPi/ARPi combinations for the various genotypes that were studied in PROPEL, MAGNITUDE, and TALAPRO2. Based on these trial data, 16% of panel members were not sure or abstained when asked whether they would offer PARPi/ARPi combination therapy to patients with *BRCA1/2*-mutated mCRPC, while the remaining 84% of panel members endorsed offering PARPi/ARPi combination therapy to these patients. By contrast, only 27% of panel members indicated that they would offer PARPi/ARPi combination therapy to patients without HRR gene mutations. The FDA decisions for olaparib plus abiraterone and talazoparib plus enzalutamide—which were released after the USPCC meeting—appear to align with the sentiments of the USPCC experts, with approvals limited to patients with *BRCA1/2* mutations (olaparib/abiraterone and niraparib/abiraterone) or deleterious HRR gene mutations (talazoparib/enzalutamide).

Theranostics and RLT.—With the approval of lutetium-177 vipivotide tetraxetan (^{177}Lu-PSMA-617) for mCRPC along with 3 prostate-specific membrane antigen (PSMA)–targeted positron emission tomography (PET) radiotracers, physicians are now faced with the need to simultaneously integrate new monitoring and treatment standards in a highly heterogeneous population. The challenges are amplified by the contrasting standards used in the 2 reference studies for ^{177}Lu-PSMA-617. In the phase 3 VISION study, ^{177}Lu-PSMA-617 with standard of care significantly improved radiographic progression-free survival (PFS) and overall survival (OS) relative to standard of care alone among patients with mCRPC who had received prior treatment with ARPis and taxanes.[17] These results are supported by the phase 2 TheraP trial, which showed that ^{177}Lu-PSMA-617 improved PSA response and

PFS outcomes compared with cabazitaxel in patients with mCRPC.[18] Both studies mandated confirmation of PSMA expression by PET/CT for eligibility; however, VISION and TheraP classified PSMA positivity differently, complicating the use of PSMA theranostics in clinical practice.

In VISION, patients were considered PSMA-positive if the maximum standardized uptake value (SUV_{max}) for at least 1 tumor lesion was greater than that of the liver parenchyma, with no PSMA-negative lesions (PSMA uptake less than the liver parenchyma) measurable by CT.[17] By contrast, the TheraP protocol used a fixed SUV_{max} cutoff of at least 20 to identify PSMA-positive lesions, excluding patients who had metastatic lesions with PSMA SUV_{max} of 10 or less. Patients with discordant (18)F-fluorodeoxyglucose (FDG)-positive and PSMA-negative lesions were also excluded in TheraP.[18] Panel members felt that the TheraP standard represented more stringent criteria that selected for a population with extremely high PSMA expression, thus accounting for the higher response rates in treated patients.[19]

USPCC experts were divided regarding the best standardized criteria for selection of patients for PSMA-targeted RLT, with 44% preferring VISION study protocol, 19% using VISION criteria for PSMA positivity but allowing PSMA-low or PSMA-negative lesions, and only 6% preferring the TheraP criteria. Although the USPCC panel included experts from many of the largest cancer centers in the United States, very few were able to support concomitant PSMA and FDG PET imaging for every patient and thus panelists felt implementation of the TheraP standard was unrealistic in routine clinical practice.

Another practical consideration related to theranostic PCa management is the use of advanced imaging techniques to monitor treatment responses. The USPCC discussed 2 types of imaging that may provide useful response information: PSMA PET/CT and single-photon emission computed tomography (SPECT)/CT obtained from ^{177}Lu-PSMA gamma emission 24 hours postinfusion, the latter of which allows for dosimetry calculations.[20] One of the potential advantages of postinfusion SPECT-based dosimetry is the potential for identification of hyper-responders or nonresponders, which could allow providers to adjust RLT dosing or switch treatments, respectively.[18,21–23] Most USPCC experts, however, emphasized the need for additional data before postinfusion SPECT is routinely integrated at every visit. PSMA PET was generally viewed as a more practical imaging option, although guidelines are conflicting regarding the use of PSMA PET to monitor response in patients receiving PSMA-directed RLT. NCCN specifies that conventional imaging should be used for treatment response monitoring, and the American Society of Clinical Oncology has recently released a Rapid Recommendation indicating that there is no role for PSMA PET monitoring in patients receiving ^{177}Lu-PSMA-617.[4,24,25] By contrast, the Society of Nuclear Medicine and Molecular Imaging Appropriate Use Criteria consider PSMA PET to be appropriate for assessing response to PSMA-based RLT,[26] and the RADAR VI panel indicated that PSMA PET may be used for treatment monitoring but should not be used alone to make decisions regarding treatment discontinuation.[27] USPCC experts were similarly divided regarding the appropriate use of PSMA PET for response assessment in patients receiving ^{177}Lu-PSMA-617: 53% of experts believed PSMA PET was appropriate for follow-up monitoring while 39% indicated PSMA PET monitoring should only be

used in research settings. If PSMA PET is used for response assessment, USPCC experts recommended consideration of conventional imaging in addition to PSMA PET every 2 to 3 cycles to monitor for mixed responses in PSMA-negative or PSMA-low lesions.

NEPC and AVPC

Aggressive variants of PCa can emerge during hormonal treatment for metastatic disease.[28] This may manifest clinically as histologic transformation from prostate adenocarcinoma to small-cell NEPC, similar to the transformation of lung adenocarcinoma to small-cell lung cancer (SCLC). Patients with small-cell NEPC are often managed using SCLC regimens (ie, first-line platinum-based chemotherapy), which is supported by NCCN guidelines.[4] However, the diagnosis of NEPC is challenging and relies on metastatic tumor biopsy. In the absence of biopsy, aggressive-variant clinical features have also been used in phase 2 trials to select patients with AVPC for platinum-based chemotherapy. The relative lack of diagnostic criteria and randomized clinical trial data complicate the management of NEPC/AVPC.

Diagnosis and Classification.—Neuroendocrine or small-cell differentiation detected on biopsy tissue remains the undisputed standard for NEPC/AVPC diagnosis. As such, the panel discussed indications for tissue biopsy to assess for the presence of NEPC/AVPC. Most USPCC experts recommended considering a biopsy to evaluate for AVPC in the following scenarios: development of new liver metastases despite low or stable PSA levels (97%), PSMA-negative soft tissue or visceral lesions (83%), and parenchymal brain metastases (61%). Only 17% of USPCC experts recommended biopsies in all patients with castration-resistant PCa.

Given the challenges of metastatic tissue biopsies, USPCC experts discussed the use of liquid biopsies as an option for diagnosing and monitoring mCRPC transformation. Not only do liquid biopsies reduce the burden of tumor biopsy but they can also be used to capture intertumoral and intratumoral heterogeneity and dynamic changes.[28,29] Commercially available ctDNA tests can identify genomic alterations enriched in NEPC/AVPC (eg, loss of *RB1*, *TP53*, and *PTEN*),[30,31] and 61% of USPCC experts indicated they use these genomic features to select candidates for platinum-based chemotherapy in patients without histologic features of NEPC on biopsy. In the future, circulating tumor cell liquid biopsies may provide an alternative to ctDNA-based techniques, more reliably identifying NEPC.[32,33] Until that time, tumor biopsy remains the standard approach.

Because NEPC/AVPC is a highly heterogeneous disease state, disease classification and standardization of nomenclature has thus far been challenging. The WHO classification system fails to capture the broad range of morphologic, genomic, and clinical features that may be present in patients.[34,35] USPCC experts emphasized the need to assess clinical features in conjunction with pathologic features (eg, morphology and immunohistochemical markers of metastatic biopsies) and molecular markers.

Systemic Therapy.—Systemic therapy for NEPC is generally based on recommendations for SCLC because of the shared pathologic and molecular features across poorly differentiated neuroendocrine carcinomas. Clinically defined AVPC has also been associated

with platinum sensitivity in phase 2 trials. In patients with de novo small-cell carcinoma, initial hormonal therapy should still be considered because of the high likelihood of mixed histologies, and ADT should be continued in those patients who develop treatment-emergent NEPC. There is evidence that cabazitaxel plus carboplatin delays progression in patients with AVPC, and this is currently the only treatment option supported by clinical trial results.[36] Because of limited data regarding NEPC/AVPC treatment, next-line therapy after progression on platinum-based chemotherapy remains uncertain. Among those who responded to the question about subsequent treatment after progression on a carboplatin doublet, USPCC experts were evenly split between lurbinectedin (17%), pembrolizumab (14%), taxane chemotherapy (14%), or other treatment (14%). In general, USPCC experts emphasized the urgent need for large, well-controlled trials in patients with NEPC/AVPC to improve the classification and treatment of this disease state.

Looking to the Future: Clinical Trial Design

In many ways, the commercial development of new management options for mCRPC has preceded definitive evidence for the application of these strategies in clinical practice. As such, USPCC experts spent considerable time discussing the need for new, thoughtfully designed studies in the mCRPC setting. When trials for many of the newly approved mCRPC drugs were initially designed, fewer treatment options were available, leading to the use of ARPis as active comparators. Many—but not all—USPCC experts felt that ARPi control arms in populations who have previously received ARPis no longer represent best standard of care because of the increasingly nuanced approach to mCRPC management. As an alternative, USPCC experts advocated for clinical trials to compare investigational therapies with physician's choice, particularly in later-line treatment settings where a number of agents are both available and reasonable. Although some USPCC experts voiced concerns about the challenges of physician's choice arms in clinical trials, including the difficulties with controlling for different comparator treatments, others pointed to the successes of recent phase 3 trials that allowed physician's choice, such as VISION and TRITON3.[14,17] Furthermore, physician's choice of treatment has been used as a comparator for more than a decade in other heavily pretreated tumor types,[37–40] suggesting feasibility with careful trial design. Advantages of physician's choice control arms with well-defined standard-of-care options include the use of treatments that are most likely to be used in real-world settings and the potential for faster trial accrual because of increased physician willingness to enroll patients in trials.

CONCLUSIONS

At the first annual USPCC meeting, our multidisciplinary group of experts identified a number of ongoing challenges with the management and monitoring of mCRPC. Given the rapid advancements in the clinical approach to mCRPC, providers who manage PCa are routinely faced with clinical decisions not addressed by the extant literature. Nonetheless, several areas of general consensus were identified among USPCC experts, including the benefits of PARPis and RLT in appropriately selected patients. Ongoing questions and controversies related to mCRPC care include optimal treatment sequencing (particularly in later lines of therapy), patient selection for PARPis and RLT, systemic treatment for

aggressive variants such as NEPC, and optimal dosing and monitoring for RLT. Ongoing clinical trials will address some—but not all—of these challenges, and future clinical trial designs should take into consideration the fast pace of development for mCRPC and the need for adaptability to ensure that study results are applicable to current clinical practice.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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