EDITORIAL

Clinical Research

Editor' summary: A paradigm shift in castration-resistant prostate cancer management

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Prostate cancer (PCa) is the most common non-skin cancer in elderly males in Western countries and despite several surgical and non-surgical therapeutic options, unfortunately, 10–20% of all patients will develop a castration-resistant status (CRPC) within 5 years from diagnosis [1, 2]. Until 2010, androgen deprivation therapy and docetaxel were the only available strategies to manage patients with metastatic CRPC [1, 2]. Afterwards, several hormonal and non-hormonal treatments such as abiraterone acetate, apalutamide, cabazitaxel, enzalutamide, darolutamide, the immunotherapeutic sipuleucel-T, the PARP inhibitor olaparib for selected men with homologous repair deficiencies, and the radiopharmaceutical radium-223, were approved after showing a significant survival benefit in patients with metastatic or non-metastatic CRPC (mCRPC) [2]. Notwithstanding all these therapeutic options, many questions remain unsolved. In this online collection (https://www.nature.com/pcan/collections), the editors of PCAN have selected ten key papers, published in the last years on our journal, which highlight and provide novel insights into important clinical and translational advances in the management of CRPC. Particularly three topics have been considered.

CONCOMITANT SEQUENTIAL TREATMENT IN CRPC

Randomized, prospective data now show that choosing an alternative approach (PARP inhibition with olaparib in eligible patients or chemotherapy with cabazitaxel in a broader population of mCRPC) is superior to sequencing from one androgen receptor treatment agent (ARTA) to the other, and a second ARTA should really not be considered the standard of care. However, even in those studies there were patients who experienced responses and some clinical benefit from the 2nd ARTA, albeit of shorter duration. Therefore, as Mori et al. [3] point out, understanding whether there is an optimal sequence may still be helpful. This meta-analysis evaluated optimal sequencing of abiraterone and enzalutamide.

Cross-resistance between abiraterone and enzalutamide is now well appreciated, leading most experts to now recommend an alternative therapy with a different mechanism of action in men with mCRPC who have progressed on a prior ARTA, regardless of whether the setting that ARTA was used. Cheng et al. [4] reported, in a 7 center multi-institutional chart review, the poor outcomes of 310 men with mCRPC based on prior exposure to abiraterone, docetaxel, neither therapies, or both prior therapies. As expected, most men who receive enzalutamide after abiraterone do not have a 30% or greater PSA decline (only 28% responded), and PFS is short (4 months). This article nicely describes that a second ARTA should only be considered in men who have exhausted other proven therapies or who are not candidates or refuse proven therapies such as docetaxel, cabazitaxel, radium-223, PARP inhibitors or PSMA-Lu177. Precision medicine approaches such as germline and somatic tumor profiling and both standard and PSMA-PET imaging can identify men who may have a greater benefit from non-cross resistant therapies.

Shore et al. [5] retrospectively evaluated real-world data on radium-223 plus abiraterone/prednisone or enzalutamide. Overall, a total of 303/625 patients (48%) received radium-223 in combination with either abiraterone/prednisone or enzalutamide and most of them (220/303; 73%) received it as a layered regimen. Pathologic fractures were reported in 10% of patients in the overall cohort, varying from 8% in the layered radium-223 and abiraterone/prednisone sub-cohort to 18% in the concurrent radium-223 and abiraterone/prednisone sub-cohort which is lower than those reported in phase III trials. This is likely due to less intensive imaging practices in the real-world settings, or perhaps due to the exclusion of fractures considered not clinically relevant, however, the higher rate (55–67%) of concomitant bisphosphonates is also likely an important contributing factor. Although this study opens new insights on the possibility to combine different treatments, it still highlights that many patients in a real-world setting do not receive-adequate bone management considering that 40–50% of the study population did not receive bisphosphonates or denosumab despite several years of androgen deprivation treatment.

NEW THERAPEUTIC OPTIONS

Germline alterations in DNA damage repair are present in up to 12% of men with metastatic prostate cancer, and somatic alterations account for another approximately 10–20%. For these patients, especially those with alterations in BRCA1 or 2, the PARP inhibitor olaparib has proven to confer a survival advantage compared to sequential ARTA based on the phase 3 PROFOUND trial [6]. Questions remain about whether alterations such as ATM or less common homologous repair genes truly predict sensitivity to PARP inhibition, although Ratta et al. [7] point out that the rare patients with PALB2 alterations had a high rate of response. This review highlights the fact that the future of PARP inhibitor therapy in mCRPC may be in combinations, with a wide variety of partners currently in clinical testing including immune checkpoint inhibitors, radiopharmaceuticals, and AR-targeted agents such as in the recently published PROPEL trial of abiraterone plus olaparib [8].

Targeted radionuclide therapy with Actinium-225-labeled PSMA ligands has emerged as a promising treatment modality in the management of mCRPC. In this systematic review by Satapathy et al. [9], 10 studies were included with 256 patients, of which 62% achieved a biochemical response of ≥50% decline of PSA, with

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pooled median progression-free survival of 9.1 months and overall survival of 12.8 months. The most common adverse event was xerostoma (72%). These data suggest that Actinium-225-PSMA radioligand therapy could be a new addition for the treatment of mCRPC, but more work will be needed to reduce these on-target toxicities to ensure tolerability long term, and comparative studies would be important to identify whether it would replace or supplement Lu177-vipivotide tetraxetan.

Radioligand therapy with Lu177-vipivotide tetraxetan is now USFDA approved and widely used in Europe and Australia for the treatment of PSMA (+) men with mCRPC who have failed at least one prior ARTA and docetaxel. In this systematic review by Calepos and colleagues [10], 10 studies were included with a total sample size of 369 patients, with a pooled any PSA decline of 68% and a >50% PSA decline in 37%. This review suggests promising results that mirror the phase 3 VISION trial [11] for the treatment of mCRPC. In terms of safety, the treatment is well tolerated however some patients may experience some grade 3–4 hematotoxicity (12–25%).

THE IMPACT OF ARTA AND TUMOR'S CHARACTERISTICS ON TREATMENT OUTCOME

Treatment emergent small cell neuroendocrine prostate cancer (t-SCNC) has been evaluated as one mechanism of androgen resistance in castration-resistant prostate cancer patients (CRPC) [12]. Diagnosis of t-SCNC is based on histologic evaluation of a metastatic tumor biopsy and accounts for about 17% in CRPC after abiraterone or enzalutamide treatment [12]. Several non-invasive methods to identify this specific aggressive PCa variant is under investigation. Aggarwal R and co-workers [13] characterize the specific clinical, genomic, and transcriptional hallmarks of men with mCRPC identified as low PSA Secretors. All patients designated as low PSA Secretors in this analysis had radiographic progression without a concomitant rise in serum PSA level defined as serum PSA < 5 ng/mL plus >5 metastases with radiographic progression at study entry, which was found to have optimal discriminatory ability for identification of a transcriptionally defined t-SCNC including RB1 loss and low AR activity. Low PSA secretors demonstrated shortened survival from the date of mCRPC compared with normal secretors (median OS = 26.7 months vs. 46.0 months). If confirmed, low PSA secretors could identify a specific sub-group of patients with a poor survival and resistant to standard treatment. The possible role of combination with other biomarkers as chromogranin or genomic profiling should be also evaluated in future clinical trials.

Enzalutamide has become a standard of care therapy by extending survival now across a range of disease states ranging from mHSPC to nmCRPC to mCRPC. A question of how patients progress on enzalutamide in terms of PSA levels and the prognostic relevance of low PSA progression was addressed by Bryce et al. [14], where it was shown that nearly 1 of 4 men progressing on enzalutamide in the PREVAIL phase 3 chemo-naïve mCRPC trial had no rise in their PSA at the time of radiographic progression. PFS was shorter in these men by 3 months, but overall survival did not differ, likely due to the effective use of subsequent therapies at radiographic progression. Many of these radiographic progression events in PSA-non-progressors were in soft tissue (37% for those with bone-only disease at baseline, 58–87% if soft tissue ± bone metastatic disease was present at baseline). These data suggest that regular imaging should be performed over time during potent AR inhibition due the frequent PSA-imaging disconnect that may occur, with major implications for missing radiographic progression. Recent data presented at ASCO 2022 based on the ARCHES trial mirror this work and suggests the need for regular imaging in men with mHSPC who are treated with potent ARSIs [15].

TP53 mutations are one of the most common somatic genetic alterations that occur in men with mCRPC and are associated with a poor prognosis and aggressive disease course. Maughan et al. [16] found that p53 loss of function as determined by p53 protein accumulation by IHC in the primary tumor was identified in 27% of 101 men with mCRPC and associated with poor survival (HR 2.3) independent of other clinical variables. While a small dataset, these data suggest that genetic information may complement and add to patient phenotypes and known prognostic factors such as patterns of spread, pain, LDH, PSA levels, KPS, and Gleason sum. The main question now is should treatment be changed based on knowledge of p53 status, such as with treatment intensification with triple chemo-hormonal therapy plus ARSI such as in the recently published PEACE-1 and ARASENS trials [17, 18]. This is not yet addressed and represents a reasonable hypothesis to test.

Since 2004, docetaxel has been a standard treatment in mCRPC, since then 6 new therapies have been shown to prolong OS in men with mCRPC (Sipleucel, Abiraterone, Enzalutamide, Radium 223, Cabazitaxel and Olaparib). Francini et al. [19] sought to evaluate the impact of these newer therapies on the OS of these men in a single institute. Looking at two different time cohorts (2004–2007 ($n = 218$) vs 2010–2013 ($n = 272$)) with an analysis endpoint of OS within 5 years after mCRPC diagnosis, patients in newer therapy era demonstrated an OS advantage (2.8 v 2.2 years) with a 41% decreased risk of death, with an extra benefit (2.7 v 2.1 years) for the patients who initially presented with de-novo metastatic disease. Here is evident that access to more effective therapies improves the median overall survival but the cumulative effect is less then hoped for or expected, possibly due to cross-resistance, limited access, or underutilization of these therapies due to costs/availability, or toxicities.

The evidence summarized in this collection highlights how treatment landscape in CRPC management has completely changed in the last 5–10 years but at the same time opens new insights in the unmet needs that remain in this area. Particularly, mechanisms of resistance, the role of next-generation imaging in this setting, optimal therapeutic sequencing or balancing patients' preferences with disease characteristics, accessibility, costs, and clinician experience are still far to be defined.

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DATA AVAILABILITY

There is no data associated with the manuscript.

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AUTHOR CONTRIBUTIONS

CDN wrote the manuscript, literature search, approved the final version. AJA revision of the manuscript, addition of references, approved the final version. IO revision of the manuscript, addition of references, approved the final version. TD revision of the manuscript, addition of references, approved the final version.

ADDITIONAL INFORMATION

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