Paradigm Changes in Prostate Cancer Management in Recent Years

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Interview Summary

This article discusses changes in the advanced prostate cancer landscape over the past decade that have induced a paradigm shift in patient management. These changes include the emergence of next-generation imaging techniques, such as multiparametric whole-body MRI (mpMRI) and prostate-specific membrane antigen positron emission tomography-computed tomography (PSMA PET-CT), and the role they play in the diagnosis, staging, and monitoring of prostate cancer.

Perhaps the most significant change to the treatment landscape, the introduction of androgen receptor-pathway inhibitors (ARPI) is described, including findings from the EMBARK and recent ARANOTE studies, and the questions they raise in terms of how we think about hormone therapy for advanced prostate cancer. The potential adverse events of ARPIs and how to manage them are also discussed.

INTRODUCTION

Prostate cancer is the second leading cause of death in adult males globally.[1] Most of these deaths are attributable to advanced disease, which can be present at diagnosis or can occur after disease relapse following local treatments (radical prostatectomy and/or radiation therapy).[2]

Relapse is indicated by biochemical recurrence of disease and may or may not be accompanied by evidence of distant metastasis.[2] Currently, the mainstay of medical treatment for disease recurrence is androgen deprivation therapy (ADT), a form of hormone therapy achieved through surgical or chemical castration.[2] In specific clinical indications, ADT may induce disease regression, relieve symptoms, and prolong survival; however, it is often used to manage biochemical recurrence after failed primary therapy despite a lack of evidence to demonstrate survival benefit in this setting.[3] ADT is associated with a broad range of adverse effects (AE), such as fatigue, depression, weight gain, increased cholesterol and triglycerides, insulin resistance, and reduced bone density, which can impact patients' quality of life (QoL).[3] In addition, prostate cancer typically develops resistance to ADT, at which point the disease transitions from hormone-sensitive prostate cancer (HSPC) to castration-resistant prostate cancer (CRPC).[4]

The most significant change to the prostate cancer treatment landscape over the last decade is the introduction of ARPIs. In patients with advanced prostate cancer, adding an ARPI such as abiraterone, apalutamide, enzalutamide, or darolutamide to standard-of-care therapy significantly extends progression-free survival, and increases overall survival (OS) in metastatic HSPC (mHSPC) by approximately 25%, without adding substantial toxicity overall.[5-10] ARPIs are now being used at many different stages of prostate cancer.[11-14] They have not only changed clinical practice but also generated new questions about the optimal treatment for prostate cancer.

Diagnosis and Staging

The emergence, over the past 15 years, of next-generation imaging techniques such as mpMRI and PSMA PET-CT have undoubtedly made an impact on prostate cancer management (Tombal, personal communication).[15] However, any discussion of their role and value in this field should consider the stage at which they are used: local staging or metastatic work-up.

Local staging

The introduction of prostate mpMRI, followed by multiple lines of consensus recommendations[16-19] on how to interpret them, has profoundly changed the way healthcare professionals (HCP) perform local staging diagnostics.[20–22] Prior to mpMRI, diagnosis of prostate cancer required invasive techniques such as digital rectal examination and transrectal ultrasound, and a biopsy was performed only if sufficient clinical suspicion of cancer existed.[22] Thus, before the routine use of mpMRI, prostate cancer diagnosis lacked a precise, strategic approach.

As a non-invasive imaging technique, mpMRI can provide information about the structure and composition of the prostate gland, which enables earlier, more accurate detection of prostate cancer.[22] This technology has also revolutionised assessment of the extent and aggressiveness of the disease, guiding treatment decisions and permitting close monitoring of treatment response.[22]

The 'multiparametric' aspect of mpMRI involves the combination of multiple imaging sequences to enhance the accuracy of cancer detection and characterisation.[22] For example, T1-weighted imaging (T1WI) can identify regional lymph nodes and skeletal metastasis, as well as the presence of haemorrhage; T2-weighted imaging (T2WI) provides information about prostate anatomy, highlighting areas that are suspicious for cancer; diffusion-weighted imaging (DWI) improves the sensitivity and specificity of T2WI; and dynamic contrast-enhanced (DCE) imaging may be useful for scoring peripheral zone lesions.[22]

The Prostate Imaging Reporting and Data System (PI-RADS) is a standardised scoring system used to interpret and report the findings from mpMRI of the prostate. Developed through consensus with prostate MRI experts, PI-RADS was initially published in 2012,[23] and most recently updated in 2019.[24] PI-RADS brought considerable precision to prostate cancer diagnosis by supporting informed biopsy decisions (Tombal, personal communication).[25] Lesions are scored on a Likert scale from 1 to 5, with higher numbers indicating greater suspicion for clinically significant prostate cancer. Lesions with a score of ≥3 are typically targeted for sampling at biopsy, whereas lesions with a score of ≤2 are considered negative.[22]

Beyond initial diagnosis and staging, mpMRI also supports the management of low-risk patients, guiding them toward active surveillance, informing decisions regarding nerve- and continence-sparing surgery, and helping to focus radiotherapy.[17,23] In intermediate-risk patients, mpMRI can evaluate minimal extra-capsular disease, and in high-risk patients, it can detect skeletal or nodal metastases.[23]

The adoption of mpMRI into clinical practice is supported by large, prospective, randomised studies, which show that it expedited time to correct treatment, with good detection of clinically significant cancers and low detection of insignificant cancers.[26-29]

Metastatic work-up

Abdomino-pelvic computed tomography (CT) and bone scintigraphy remain the standard diagnostic imaging modalities at diagnosis.[15,25] Their diagnostic performance, however, is limited.[15,25] Besides PET-PSMA, whole-body MRI is another one-stage all-in-one imaging technology with superior diagnostic accuracy for detecting metastases.[30]

PSMA PET-CT involves the use of a radiotracer that binds to the PSMA protein, producing an image that is highly sensitive and specific for the detection of prostate cancer.[22] This means the technique can detect small metastatic lesions that would be undetectable using conventional imaging techniques, or those located at atypical body locations.[22] There is considerable interest among prostate cancer specialists to introduce PSMA PET-CT into the clinical pathway,[31] and European guidelines now recommend its use for metastatic screening in patients with high-risk localised disease or locally advanced disease.[25] Guidelines from the USA National Comprehensive Cancer Network (NCCN) also suggest that PSMA PET-CT can serve as a more effective frontline imaging tool at both initial staging and biochemical recurrence compared with CT or MRI.[32]

The increased use of PSMA PET-CT is anticipated to result in more patients being diagnosed with early metastatic disease, yet the clinical benefit of detecting metastases at an earlier time point remains somewhat unclear.[2,33] Both diagnostic accuracy and clinical utility need to be carefully considered when changes are made to imaging techniques used in clinical practice (Tombal, personal communication).

As an example, a 65-year-old patient with locally advanced prostate cancer might typically be treated with radiotherapy and 2 years of hormone therapy. However, if next-generation imaging techniques such as PSMA PET-CT are applied and they identify a small number of lymph-node metastases, the patient might be reclassified as metastatic, indicating lifelong combination hormone therapy.

Yet, there remains little-to-no evidence in the literature that such a low burden of lesions will negatively impact the patient's OS, and the additional treatment will expose them to more adverse events (Tombal, personal communication). The problem is that the current evidence for treatment recommendations is based on disease staging using conventional imaging techniques.[31]

The danger of applying new imaging modalities without an understanding of their impact on patient outcomes from systemic analyses of data is that it could lead to overtreatment. Another example is a patient diagnosed with two metastases on a bone scan, who would typically be treated with ADT plus one ARPI, and prostate radiotherapy would be discussed. If the same patient receives a PSMA PET-CT, which shows five-to-six metastases, that patient would now be classed as having 'high-volume' metastatic disease and might then be treated with docetaxel (Tombal, personal communication). Yet, there is limited evidence to suggest that docetaxel improves absolute effects at 5 years in patients with 'low-volume' metastatic disease (assessed by conventional imaging).[34-37]

INITIAL TREATMENT

Perhaps the most significant paradigm shift in early treatment for prostate cancer came from the EMBARK study.[38] Prior to EMBARK, it was challenging to know how to manage biochemical recurrence of localised prostate cancer that has failed all options for local treatment.[39] There are no studies that definitively show that starting ADT treatment immediately can improve OS at this stage, and it is known that long-term ADT is associated with side effects.[39] Therefore, physicians generally agreed that strategies such as metastatic-directed therapy to delay initiation of ADT were acceptable in low-risk patients.[39] The question in most physicians' minds then was 'when' should hormone therapy be started? (Tombal, personal communication).

EMBARK aimed to evaluate 'how' hormone therapy should be used rather than 'when' it should be initiated.[38] The objective of EMBARK was to compare the efficacy and tolerability of ADT alone, ADT plus enzalutamide, and enzalutamide monotherapy in patients with prostate cancer who have had high-risk biochemical recurrence.[38]

An outcome from EMBARK which potentially changes established clinical practice is that not only was ADT plus enzalutamide more efficacious in this population versus ADT alone (hazard ratio [HR] for metastasis or death: 0.42; $p<0.001$), but enzalutamide monotherapy was also more efficacious versus ADT alone (HR for metastasis or death: 0.63; $p=0.005$).[39] This changes the question for systemic treatment from 'when should ARPI be added to ADT' to 'when should ADT be added to ARPI' and further studies are needed to answer this question.[39]

The second significant result of EMBARK is that it raises the following question: with evidence showing that enzalutamide has a positive impact on metastasis-free survival in patients with high-risk biochemical recurrence while maintaining overall QoL over 5 years, is it still acceptable to use strategies to delay hormone therapy?[38,39]

One of the key characteristics of the EMBARK study design was the suspension of treatment at Week 37 for patients whose prostate-specific antigen (PSA) level dropped below 0.2 ng/mL. Treatment was restarted when PSA levels increased to at least 5.0 ng/mL (in patients without radical prostatectomy) or at least 2.0 ng/mL (in patients with radical prostatectomy).[38] During the study, 90.9% of patients in the ADT plus enzalutamide group had treatment suspended for a median of 20.2 months, 67.8% of patients in the ADT alone group had treatment suspended for 16.8 months, and 85.9% of patients in the enzalutamide monotherapy group had treatment suspended for a median of 11.1 months.[38] The authors of the study suggest that the shorter duration of treatment suspension with monotherapy was likely due to a lack of testosterone suppression in that arm.[38]

With evidence that enzalutamide monotherapy has a positive impact on metastasis-free survival,[39] it is prudent to consider the safety profile with long-term

treatment. In the enzalutamide monotherapy arm of EMBARK, the most common adverse events were gynaecomastia, fatigue, arthralgia, hot flashes, and hypertension.[38] Overall, 17.8% in the enzalutamide monotherapy group permanently discontinued treatment due to an AE.[38] However, data from EMBARK suggest that treatment suspension may have the potential to optimise enzalutamide monotherapy by alleviating long-term adverse events, among patients who meet a predefined PSA threshold.[40]

TREATMENT INTENSIFICATION WITH ANDROGEN RECEPTOR-PATHWAY INHIBITORS

Initially, ARPIs were evaluated in the post-docetaxel metastatic CRPC (mCRPC) setting, but subsequent studies showed that they are also associated with improved outcomes in the mHSPC and non-metastatic CRPC (nmCRPC) settings.[41] While treatment intensification with ARPI combinations is now the most preferred line of treatment in patients with mCRPC,[42] they remain relatively underutilised in nmCRPC and mHSPC.[33,43] The use of ARPIs is slowly increasing in these settings, following changes to guidelines and growing awareness among HCPs.[33,43]

The earlier use of ARPIs in the treatment pathway has resulted in profound responses in patients with advanced prostate cancer.[2,44] Patients with nmCRPC tend to be asymptomatic at diagnosis,[33] and delaying the appearance of metastases is linked to the development of symptoms and, therefore, impact on QoL.[2] The use of ARPIs in both nmCRPC and mHSPC has been associated with a preservation of health-related QoL over the long term (prescribers should check licensed indications for individual ARPIs).[2,45]

Patients with advanced prostate cancer were traditionally treated by a urologist until progression to mCRPC, when care was transferred to a medical oncologist.

However, as the treatment landscape has become more complex, practice patterns and attitudes have adapted, and the lines between these specialties have blurred.[46] As ARPIs are now treatment options at various stages of advanced prostate cancer, they can, and should, be prescribed by urologists, radiation oncologists, and medical oncologists where appropriate (Tombal, personal communication).

At the latter end of 2024, primary data were published from the ARANOTE clinical study, which evaluated darolutamide plus ADT versus placebo plus ADT in patients with mHSPC.[9] Darolutamide is structurally different from other ARPIs, making it less likely to cross the blood–brain barrier, according to animal models, and reducing the potential for drug–drug interactions.[9] Darolutamide is now licensed in mHSPC in combination with ADT and may present an additional therapeutic option for this patient population in the future.[14]

ARANOTE showed that darolutamide plus ADT significantly improved radiological progression-free survival (rPFS) in patients with mHSPC, reducing the risk of radiological progression or death by 46% versus placebo plus ADT (HR: 0.54; 95% CI: 0.41–0.71; p<0.0001).[9] No statistically significant benefit for overall survival was shown for darolutamide versus placebo at the final analysis (HR: 0.78; 95% CI: 0.58–1.05).[47] In the earlier TITAN study, the reduction in risk of rPFS in patients with mHSPC with apalutamide versus placebo was 52% (HR: 0.48; 95% CI: 0.39–0.60; p<0.001), and in the ARCHES trial, the reduction in risk of rPFS in patients with mHSPC with enzalutamide versus placebo was 61% (HR: 0.39; 95% CI: 0.30–0.50; p<0.001).[5,8] Network meta-analyses have attempted to compare the efficacy of the different ARPIs in combination with ADT versus ADT alone,[48,49] but without head-to-head studies, indirect comparisons, such as matching-adjusted indirect comparisons (MAIC), may be required to compare these therapeutic options in mHSPC.[50] In a Phase II, head-to-head cross-over trial in patients with mCRPC (ODENZA), PFS rates were 83% (95% CI: 76–89%) with darolutamide and 88% (95% CI: 81–93%) with enzalutamide.[51]

MANAGING ANDROGEN RECEPTOR-PATHWAY INHIBITOR TOXICITY

Whilst the addition of ARPIs to ADT generally increases overall health-related QoL and prolongs the time to first deterioration of pain/fatigue compared with ADT alone,[45] there are some AEs specifically associated with ARPI therapy that require management to optimise treatment in patients with advanced prostate cancer.[52] These AEs include fatigue, hypertension, bone fragility, seizures, neurocognitive effects, rash, and hot flashes.[2,12-14] Of all the ARPIs, darolutamide is considered to be associated with the fewest AEs;[53] however, although ARPIs share the same mechanism of action, caution should be used when comparing AEs across different studies in the absence of head-to-head comparative studies.[2,54]

Fatigue

Fatigue is a common adverse reaction to some ARPIs.[12-14] Patients should be informed that there is an adjustment phase of perhaps 4 months, during which they may experience fatigue,[55] and that there are lifestyle changes that can help to alleviate this symptom.[53] Temporary suspension of treatment and or dose adjustment can also be considered.[53]

Hypertension

Hypertension is perhaps the most concerning adverse reaction associated with ADT and some ARPIs,[12-14] because of the strain it places on a patient's cardiovascular system. Roughly two-thirds of patients with metastatic prostate cancer experience clinically relevant hypertension related to treatment with ARPIs, particularly with enzalutamide.[54,56] However, in another analysis, the risk of hypertension, diabetes, or cardiovascular disease requiring an emergency room visit or hospitalisation was higher with abiraterone than with enzalutamide.[57]

Many patients with advanced prostate cancer may already be receiving anti-hypertensive medication before starting hormone therapy,[56] and interestingly, two retrospective studies have suggested that concomitant treatment with antihypertensives may be associated with longer OS on ARPIs.[58,59]

The risks of hypertension can be managed by monitoring patients' blood pressure during treatment and by considering treatment suspension or dose adjustment where appropriate.[11,12] Prescribing HCPs should inform the patients' general practitioner (GP) or primary physician that ARPIs can be associated with hypertension, and ideally, patients treated with ARPIs should also self-monitor their blood pressure at home (Tombal, personal communication).

Bone Fragility

An increased risk of fractures is common to all ARPIs.[11-14] Patients should be monitored for their fall and fracture risk before and during treatment with any ARPI, and managed according to established treatment guidelines.[12,60] The use of bone-targeted treatments to support skeletal health should be considered.[12,60]

Cognitive Changes

Treatment with ARPIs can be associated with cognitive changes, more so with enzalutamide, though studies vary in terms of the clinical significance of the differences between ARPIs.[13,61-64] Cognitive effects may be related to variable penetration of the blood-brain-barrier by ARPIs.[2]

As with other potential AEs, it is important to inform patients of the risk of cognitive changes. It seems to be rare for a patient to experience severe cognitive changes during ARPI treatment, but if this does occur, treatment should be stopped (Tombal, personal communication).

Rash

The development of a skin rash has been reported with ARPI treatment,[11,12,14,60] and it is unclear why this may occur.[2] Rash and subcutaneous skin disorders are more common with apalutamide than other ARPIs.[65,66] Treatment options for patients

with a skin rash include antihistamines, corticosteroids, dose reduction, and drug interruption.[2]

Hot Flashes

Hot flashes have been associated with some ARPIs, and they are also one of the most frequent AEs occurring with ADT.[12,13,53,67] In patients who experience frequent hot flashes, lifestyle modifications are typically the first approach to management.[53] Several medications have also been assessed in small studies to improve hot flashes, though the evidence to support their use is limited.[53]

The key to managing these potential AEs is communication: informing the patient and their GP of the risks, monitoring requirements, and advice regarding preventative measures (Tombal, personal communication).

CONCLUSION

The last 10 years have ushered in profound changes in advanced prostate cancer management. Next-generation imaging techniques have emerged that impact how we diagnose, stage, and monitor prostate cancer.[15] For local staging, mpMRI has improved the detection of prostate lesions, leading to corresponding improvements in patient care.[20-22,25-29] Although PSMA PET-CT undoubtedly increases the detection of metastatic lesions, this imaging technique requires further evaluation to determine its impact on the prostate cancer diagnosis and treatment paradigm.[22,25,31,33]

The most significant change to the treatment landscape in recent years is the introduction of ARPIs, which, when added to ADT, improve OS at many stages of advanced prostate cancer.[11-14,68] The recent ARANOTE study demonstrated that darolutamide plus ADT significantly improved rPFS in patients with mHSPC, although no statistically significant improvement in OS was demonstrated at the final analysis.[9,47] EMBARK showed that enzalutamide monotherapy may be more efficacious than ADT alone in patients with localised disease with biochemical recurrence, raising the question of whether it is still acceptable to delay hormone therapy in patients that could benefit from it.[38,39]

Whilst the addition of ARPIs to ADT generally increases overall HR-QoL compared with ADT alone,[45] ARPI therapy nonetheless increases the risk of specific AEs.[52] It is, therefore, important that both physicians and their patients are aware of these risks and that they are managed accordingly to ensure optimum treatment outcomes (Tombal, personal communication).

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