Androgen Deprivation Therapy in Prostate Cancer: A Practical Approach to Complex Clinical Scenarios

This promotional industry symposium took place during the Global Congress on Prostate Cancer (PROSCA) 2023, held in Málaga, Spain, 29th–30th November 2023

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Disclaimer:	The opinions expressed in this article belong solely to the named speakers. ORGOVYX (relugolix) is indicated for the treatment of adult patients with advanced hormone-sensitive prostate cancer. If you are a HCP in the EU, prescribing info can be found here. If you are a HCP in the UK, prescribing info can be found here.
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Meeting Summary

Androgen deprivation therapy (ADT) has been a cornerstone in the treatment of advanced prostate cancer (PCa) for many years, and continues to form the basis of current therapeutic approaches. However, a recent dramatic upsurge in the number of treatment options available in this area creates a responsibility for healthcare professionals to carefully select optimal drugs and combinations of drugs, to ensure the best outcomes and greatest quality of life for all patients. This requires a thorough understanding of clinical trial data, and an ability to apply this knowledge to everyday clinical practice. This article summarises presentations delivered during a symposium held on 29th November 2023 at the Global Congress on Prostate Cancer (PROSCA) 2023 in Málaga, Spain, where three distinguished speakers described and explored practical approaches to the use of ADT in complex clinical scenarios. Nazareno Suardi, Associate Professor of Urology at the University of Brescia, Italy, described approaches to manage ADT prescription when a patient presents with cardiovascular (CV) risk factors. Matthias Saar, Director and Chairman of the Department of Urology and Uro-oncology at the University Hospital Aachen, Germany, explored whether intermittent ADT remains an alternative in the new era of hormonal therapy. Alison Birtle, Consultant Clinical Oncologist at the Rosemere Cancer Centre, Lancashire Teaching Hospitals NHS Trust, Preston, UK, investigated the importance of drug choice in triplet or doublet therapy in patients with metastatic hormone-sensitive PCa (mHSPC). The meeting was chaired by Antoni Vilaseca, Senior Specialist in the Urology Service at the Hospital Clinic, University of Barcelona, Spain, who introduced the symposium, and also co-ordinated a question and answer session to conclude the meeting.

Introduction

Vilaseca opened the meeting by reminding the audience that the management and treatment of advanced PCa has seen a revolution over the past few years.[1] Advances include the development of new imaging techniques to support improved diagnosis of the disease, as well as the progressive introduction of new treatment approaches, from docetaxel through to poly(ADP-ribose) polymerase (PARP) inhibitors and radioligands.[1-3] Vilaseca noted that many of the new treatments have been added to standard ADT, which remains the cornerstone of treatment of advanced PCa.[3]

In the Accord Healthcare-sponsored symposium, 'Androgen deprivation therapy in prostate cancer: a practical approach of complex clinical scenarios', delivered on 29th November 2023 at the PROSCA and BLADDR 2023 hybrid meeting in Málaga, Spain, speakers from Italy, Germany, and the UK described practical approaches to ADT therapy in a series of complex clinical scenarios. The symposium aimed to help delegates update their knowledge on ADT; understand the different therapeutic options available; consider the practical challenges of ADT; and use recommendations from the European Association of Urology (EAU), and other scientific societies, to evaluate the impact on clinical practice.

Vilaseca noted that, as the population ages, the diagnosis of PCa is becoming more common in older males, many of whom are likely to have comorbidities. The first presentation of the symposium examined the use of ADT among patients presenting with CV risk factors, and the issues that should be considered in this situation. Use of intermittent ADT in the new era of hormonal therapy was discussed next, followed by an exploration of drug choice in triplet or doublet therapy among patients with mHSPC. As well as presenting the latest data to outline current opinion in this field, the speakers also ensured wider audience participation through the use of real-world case studies, designed to explore the practical applications of recent developments, with audience polling used throughout the presentations.

An initial poll revealed that the audience consisted predominantly of urologists (54%), followed by other specialities (17%), radiation oncologists (15%), medical oncologists (8%), and pharmacists (5%). There were no nurses in the audience. Overall, 84% of audience members confirmed that they use ADT in daily practice.

How to Manage Androgen Deprivation Therapy Prescription When a Patient Presents with Cardiovascular Risk

To provide context around the use of ADT in patients with CV comorbidities, Suardi began his presentation by describing the case of a 76-year-old retired truck driver with a 30-year history of smoking and recurrent PCa. His medical history included appendectomy, asthma, and hypertension, with a myocardial infarction (MI) 10 years previously. An earlier sextant biopsy showed Gleason 3+3 PCa in seven of 12 cores. The patient underwent low dose rate brachytherapy (^{125}I; 145 Gy) with no perioperative complications, resulting in a fall in prostate-specific antigen (PSA) level from 6.7 ng/mL to 2.1 ng/mL within 6 months. However, biochemical recurrence was observed from early 2023, with a relatively rapid PSA doubling time of 7.9 months. The patient's International Prostate Symptom Score (IPSS) was 19 on α-blocker treatment.

The majority (77%) of the audience voted that imaging should be the next step for this patient, followed by ADT (11%), prostatic biopsy (9%), or PSA surveillance (3%). Saar's preferred option was prostatic biopsy to detect local occurrence in addition to a PET scan, while Birtle noted that she would require additional information before deciding whether to suggest imaging or biopsy, and whether the patient would be well enough to undergo future salvage treatment.

Like the audience, Suardi opted for a fluorine-18 prostate-specific membrane antigen (PSMA) CT/PET scan without biopsy. This revealed a prostatic recurrence with left seminal vesicle invasion, and a suspicious left obturator node and para-aortic nodes. The audience broadly disagreed over the preferred next step, with 43% opting for ADT, 27% for radiation therapy, 15% for prostatic biopsy, 9% for surgery, and 6% recommending observation until further symptoms. Vilaseca noted that he would need to prescribe ADT, but would also consider radiation therapy depending on the volume of disease. Saar described his preference for a systemic approach, including ADT, if this was acceptable, with additional androgen receptor signalling inhibitor (ARSi) treatment. Birtle observed that, as the patient was already symptomatic with a high IPSS on α-blockers and a rapid PSA doubling time, she would need to determine if she could deliver an appropriate dose of radiotherapy, and would also treat his retroperitoneum. She would consider ADT, but also introduce an ARSi.

Suardi noted that the evidence for hormonal therapy for relapsing patients from the EAU guidelines is not particularly strong, with existing studies reporting conflicting results.[4] Once the decision to proceed with ADT therapy had been made, 54% of the audience would choose a luteinising hormone-releasing hormone (LHRH) agonist, 26% would opt for an oral LHRH antagonist, and 17% would choose an injectable LHRH antagonist.

Suardi reminded the audience that there is only little or no difference in efficacy between LHRH agonists and antagonists, in terms of controlling testosterone levels,[5-7] or preventing PSA progression.[7,8] However, there appears to be some disparity between the two drug classes in terms of CV risk. This was first noticed in a 2006 study of 73,196 patients with locoregional PCa, which showed an elevated risk of MI, sudden cardiac death, and coronary heart disease among those receiving agonist therapy.[9] A later analysis of pooled data from six Phase III prospective randomised trials confirmed that the risk of cardiac events was significantly lower among males with pre-existing CV disease (CVD) treated with antagonist versus agonist therapy within 1 year of initiating treatment.[10]

The PRONOUNCE trial was initiated to try to replicate these results by comparing the impact of degarelix, an LHRH antagonist, and leuprolide, an LHRH agonist, on the occurrence of CV events in patients with PCa and CVD.[11] Unfortunately, this study was terminated prematurely because of the low number of participants and events, and the lack of difference in CV events at 1 year between the two groups.

In 2020, the first oral antagonist available for the treatment of advanced PCa was investigated in the Phase III HERO trial comparing relugolix (120 mg orally, once daily) against leuprolide (injections every 3 months) among patients with advanced PCa.[12] Relugolix was shown to be highly effective in achieving a rapid and sustained castration rate, with a post hoc analysis revealing a significantly lower incidence of major adverse CV events (MACE) versus leuprolide. In particular, only 3.6% of patients with history of MACE who received relugolix experienced a further MACE, compared with 17.8% of patients who received leuprolide.[12]

The reduced CV risk of LHRH antagonist versus agonist therapy in patients with PCa with and without previous CVD has further been confirmed in a population study,[13] as well as meta-analyses.[6,8] In addition, two ongoing trials, REVELUTION and REPLACE-CV, are evaluating the CV side effects of relugolix versus leuprolide among their primary outcomes.[14,15]

The 2022 European Society of Cardiology (ESC) guidelines on cardio-oncology recommend that a baseline CV risk assessment should be performed in patients without pre-existing CVD before starting ADT. In addition, antagonist therapy should be considered in patients with pre-existing symptomatic coronary artery disease, and an annual CV risk assessment is recommended during ADT, whether with an agonist or antagonist.[16]

Suardi concluded by returning to his case study, and revealed that the patient had been initiated on degarelix (two injections of 120 mg, then 80 mg every 28 days).[17] After 3 months, the patient's PSA was 0.2 ng/mL, and testosterone level was 0.18 ng/dL. It is likely that the patient will require further treatment intensification. Suardi noted that the recent EMBARK study clearly showed that the addition of ARSi to ADT may improve metastasis-free survival in patients with biochemical recurrence of PCa.[18]

Intermittent Androgen Deprivation Therapy in the New Era of Hormonal Therapy: Still an Alternative?

Saar began by observing that mHSPC is now typically treated with combination therapy.[19] He noted that the landmark outcome studies of mHSPC reveal that attainment of very low PSA levels (≤0.2 ng/mL) after 6–12 months of therapy is associated with good prognosis, suggesting promise for an intermittent approach.[20-25] Furthermore, in the TITAN trial, patients who achieved PSA ≤0.2 ng/mL had improved overall survival (OS), as well as a prolonged time to PSA progression, and time to castration resistance.[25]

Despite the efficacy of ADT, fatigue remains an important issue for patients, irrespective of whether this treatment is used alone, or in combination with an androgen receptor inhibitor. For example, the ENZAMET trial showed that enzalutamide combination therapy was associated with greater fatigue than control, irrespective of early chemotherapy with docetaxel, although this effect did not worsen over time.[26]

Intermittent and continuous therapy have been compared in a number of trials. The randomised SWOG 9346 study, in which patients with PCa in whom PSA had fallen to <4 ng/mL following 8 months of ADT, were randomised to continuous or intermittent treatment, failed to show non-inferiority for intermittent therapy for OS.[20] However, patients with a low performance status seemed to gain a small benefit from the intermittent approach.[20] A population-based analysis of 9,772 patients with advanced PCa aged ≥66 years showed that intermittent ADT was associated with a 36% lower risk of serious CV events, 38% reduced risk of heart failure, and 48% lower risk of pathologic fracture versus continuous ADT.[27] In addition, it has been shown that an intermittent approach offers benefits in terms of mental health, physical functioning, erectile function, and libido.[20,28] The randomised ICELAND trial also showed that intermittent and continuous hormone therapy had similar efficacy, tolerability, and quality of life profiles in patients with relapsing M0 or locally advanced PCa,[29] further suggesting that intermittent therapy may be a valid option for selected patients.

It is also interesting to consider whether it is possible to pre-stratify patients as part of an intermittent approach. Data from SWOG 9346 revealed that patients with PSA ≤0.2 ng/mL achieved a median OS of 75 months, compared with 44 months and 13 months for patients with 0.2<PSA≤4.0 and PSA >4.0, respectively, following 7 months of ADT.[30]

The issues described were explored through the case of a 69-year-old patient diagnosed with PCa in 2015, with a Gleason score 4+3 prostate cancer, and an initial PSA of 20.8 ng/mL. He underwent radical prostatectomy with extensive lymphadenectomy. No positive lymph nodes were identified, but local progressive pT3b prostate cancer was observed with a very low R1 margin. The patient underwent PSA surveillance, with a PSA of 0.4 ng/mL reported in 2017, after which he underwent pelvic irradiation. In 2020, the patient presented again with a PSA of 11 ng/mL. A bone scan and CT scan of the abdomen were negative for metastases.

The vast majority (84%) of the audience voted for next generation imaging (PET) for this patient, with 8% opting for continuous ADT, 5% for ADT plus a new hormonal agent (with or without chemotherapy), and 3% opting for intermittent ADT. Birtle commented that she would start the patient on ADT and monitor his PSA kinetics, assuming he had not had a PSMA PET, and that he had a short PSA doubling time.

Saar noted that the European Society for Medical Oncology (ESMO) recommends that males with high risk of biochemical relapse starting ADT in the absence of metastatic disease should be offered intermittent, rather than continuous, treatment.[31] National Comprehensive Cancer Network (NCCN) guidelines recommend that patients who choose ADT should consider intermittent ADT, and this should therefore be discussed with the patient. However, Grade Group 4 or 5 patients should be given continuous treatment, because they show a very short response on ADT alone.[32] Once the decision to adopt intermittent therapy has been taken, Saar observed that relugolix becomes a good treatment option, as demonstrated by the HERO study described earlier, which showed that, as an oral ADT, relugolix provides a more rapid testosterone recovery compared with leuprolide (54% relugolix versus 3% leuprolide patients returned to a normal plasma testosterone level within 3 months of treatment discontinuation; P=0.002).[12]

Returning to the case study, Saar explained that the patient was given a PSMA PET scan, which revealed retroperitoneal lymph node metastases, iliac lymph node metastases, and one cervical lymph node. Sixty-nine percent of the audience voted for ADT plus a new hormonal agent at this stage, with 16% selecting ADT plus new hormonal agent with chemotherapy. Saar noted that this would be consistent with the guidelines.

Saar next presented data from the EMBARK trial mentioned previously, showing that 91% of patients on enzalutamide combination treatment with leuprolide achieved PSA <0.2 ng/mL.[33] Median duration of treatment suspension was 20.2 weeks, compared with 16.8 weeks for leuprolide, and 11.1 weeks for enzalutamide monotherapy. The overall incidence of adverse events was comparable between relugolix and leuprorelin.

Studies on next-generation intermittent ADT with ARSI are currently ongoing, including the Phase II A-DREAM study (NCT05241860), investigating treatment interruption in patients with mHSPC who have responded exceptionally well to 18–24 months of intense ADT;[34] and the pragmatic Phase III EORTC study, De-Escalate (EORTC-2238), comparing intermittent with continuous maximum androgen blockade.[35] Two further trials have investigated metastasis-directed therapy, although neither included ADT. The STOMP trial showed longer ADT-free survival for metastasis-directed therapy versus surveillance alone in asymptomatic oligometastatic PCa recurrent patients.[36] ORIOLE revealed that stereotactic ablative radiotherapy improved progression-free survival and distant metastasis-free survival, and was enhanced by total consolidation of disease identified by PSMA-targeted PET.[37]

In the future, it is clear that ADT monotherapy will no longer be an option, even for intermittent therapy, and it will therefore be important to consider combination therapies and off-treatment phases. Other strategies for the future include identifying predictors of the optimal patient, implementing metastasis-directed therapy for best responders,

and incorporating new therapies beyond testosterone-lowering agents.

Metastatic Hormone-Sensitive Prostate Cancer: When Choosing Treatment, Every Drug Matters in Triplet or Doublet Therapy

Birtle opened her presentation with the observation that all trials of systemic ADT therapy over the last 10 years have shown a survival benefit.[35] However, she noted that this puts the emphasis on clinicians to choose the optimal treatment for patients, based on the drug characteristics, toxicity, logistics, comorbidities, and patient preferences. She illustrated this point with the case study of a very fit 73-year-old male who presented with visible haematuria. He had elevated PSA (18 ng/mL) with pelvic nodes on imaging. Initial biopsies showed a Grade Group 4 tumour with heavy involvement, while imaging revealed high-volume disease with bone metastases. Saar commented he would choose triple therapy for this patient, while the audience was largely split between doublet (45%) and triplet therapy (48%).

Birtle explained that she also opted for triplet therapy with darolutamide and six cycles of docetaxel, beginning in January 2023. Although the patient experienced Grade 1 fatigue, his PSA fell to 0.1 ng/mL by September 2023. Birtle noted that her treatment choice was supported by the ARASENS clinical trial, which reported 62.7% OS at 4 years for darolutamide triple therapy, compared with 50.4% for ADT plus docetaxel in patients with mHSPC, with prolonged time to pain progression and first symptomatic skeletal event.[38] The benefit of triple therapy appears to be greatest in those with high-volume disease, defined visceral metastases, and/or ≥4 bone metastases, with ≥1 beyond the vertebral column/pelvis.[39] As the addition of darolutamide does not increase toxicity, ARASENS demonstrates that patients live longer on triple therapy with a good quality of life.[38]

Current treatment guidelines strongly support the use of triplet therapy in patients who would previously have been good candidates for docetaxel.[4,35,40,41] For patients with low volume disease, the addition of local radiotherapy should be considered, based on data from STAMPEDE showing an OS improvement for these patients.[42]

Birtle commented that, while recent advances have been remarkable, there is still more to do for patients presenting with *de novo* high-volume metastatic disease and no prior treatment, who still have poor survival.[43] The ENZAMET study revealed that treatment intensification may be required, particularly for males who are progressing at the first scan on single agent treatment or ADT plus docetaxel, providing a window of opportunity where triplet therapy may be beneficial.[44] The ARCHES trial also confirmed that patients should not be treated with ADT alone, as adding enzalutamide to ADT significantly reduced the risk of radiographic disease progression or death by 61%, compared with ADT alone.[45]

At the Advanced Prostate Cancer Consensus Conference (APCCC), the only consensus reached regarding docetaxel fitness was that patients are not fit to receive docetaxel if they have an Eastern Cooperative Oncology Group (ECOG) performance status of 3, or severe hepatic impairment.[46]

Birtle next considered which specific ADT drug should be used for optimal benefit. She noted that she is not able to use relugolix at the moment in the UK, but that this would typically be used in patients with very high-volume disease, or significant CV risk factors. She reminded the audience of the HERO study, showing that relugolix was non-inferior to leuprolide for sustained castration rate,[12] with a post hoc analysis revealing that castration rates with relugolix were similar irrespective of the concomitant use of enzalutamide or docetaxel.[47] Birtle also noted that the decision regarding which ARSi to use would depend on toxicity, efficacy, tolerability, drug–drug interactions, and reimbursement issues, while the CV risks would clearly need to be considered, as discussed previously.[12] In terms of new combinations of therapies, studies have shown no safety signals either for the combination of relugolix with enzalutamide or docetaxel,[47] or for relugolix with abiraterone or apalutamide.[48]

Relugolix also allows rapid recovery of testosterone levels after drug cessation, allowing quality of life to be restored.[12]

In the future, Birtle recommended that treatment should be escalated for high-volume patients with *de novo* metastatic disease who require treatment intensification, but de-escalated for good treatment responders.[20] She also noted that PSA levels are an excellent prognostic indicator for survival, allowing the decision to de-escalate to be taken where appropriate.[49,50]

Birtle concluded by reminding the audience that some patients may relapse on an ARSi and require more treatment than others.

She commented that patients who would previously have been candidates for docetaxel (those with visceral disease, high lactate dehydrogenase, marrow infiltration, and high-volume disease) should now be offered triplet therapy. Furthermore, although many new drugs are now available, it is important to ensure that all patients continue to receive ADT; this will require a degree of patient education once oral ADT treatments become more accessible. Finally, as treatment responders may achieve a long life expectancy following diagnosis, and treatment duration may therefore be long, it is vital to consider the choice of each drug carefully to ensure adherence, and maintain quality of life.

Conclusion

Treatment of PCa has undergone a revolution in recent years, with the availability of novel imaging techniques and new treatments transforming the prospects for many patients. While ADT with an LHRH agonist has been the bedrock of therapy until recently, the advent of LHRH antagonists, including relugolix (currently the only available oral treatment), has provided new therapy options in PCa, with benefits in terms of CV risk, quality of life, and flexibility of treatment.

The presentations given as part of this symposium provided an opportunity for experts to share their clinical practice regarding the use of ADT in complex clinical scenarios, through the sharing of data and a discussion of case studies involving a patient with a history of CV disorders, a patient with fatigue, and a patient with newly diagnosed mHSPC, for whom combination therapy including an ADT was indicated.

EU Orgovyx SmPC:
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