HORMONAL THERAPIES FOR PATIENTS WITH ADVANCED PROSTATE CANCER

***Cora N. Sternberg,[1] Bertrand Tombal[2]**

1. Department of Medical Oncology, San Camillo and Forlanini Hospitals, Rome, Italy
2. Institut de Recherche Clinique (IREC), Cliniques universitaires Saint-Luc, Brussels, Belgium
**Correspondence to cnsternberg@corasternberg.com*

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ABSTRACT

Prostate cancer (PCa) is the second most common cancer in men, comprising 15% of new cancer cases. While most cases are diagnosed at an early stage and can be managed conservatively or by local treatment alone, up to 30% of patients will receive androgen deprivation therapy (ADT). Indeed, high-risk localised and locally advanced PCa require either surgery or ADT in combination with radiation as a local strategy. On the other hand, metastatic patients are treated upfront with ADT, eventually combined with docetaxel, as suggested by recent studies.

ADT has been in use for more than 60 years and during this time it has undergone considerable evolution. Gonadotropin-releasing hormone (GnRH) agonists have supplanted surgical castration and oestrogens, and are now challenged by GnRH antagonists. ADT induces profound but often short-lasting responses. In a low serum testosterone environment, the androgen receptor (AR) pathway may be reactivated either by overexpression, by mutation of the AR itself, or by adrenal or intracrine production of androgens. These mechanisms underlie the development of the majority of castration-resistant prostate cancers (CRPCs). In addition to AR adaptation, several AR-independent mechanisms may also underlie progression of these cancers on ADT.

A new generation of AR-pathway inhibitors have succeeded first-generation anti-androgens and steroids, and are proven to extend survival in patients with metastatic CRPC. This review aims to summarise the current standard of care and available hormonal strategies in advanced PCa and future therapeutic perspectives that could change treatment paradigms in the coming years.

Keywords: Prostate cancer (PCa), androgen deprivation therapy (ADT), anti-androgens (AAs), novel anti-androgen therapies, advanced prostate cancer.

INTRODUCTION

Prostate cancer (PCa) is the second most common cancer in men, comprising 15% of new cancer cases worldwide. This amounts to an overall 5-year prevalence of 1.3 million in Europe and 3.8 million worldwide.[1,2] The 5-year relative survival rate in Europe has significantly improved over the last two decades, possibly due to increased use of prostate-specific antigen (PSA) testing, which has led to higher rates of early detection and access to healthcare resources.[3] While most cases are diagnosed very early in the disease and are either treated with local treatment (i.e. prostatectomy or radiation therapy) or managed conservatively, 7–10% of patients[4,5] present with metastatic PCa at diagnosis. Moreover, up to 40% of high-risk localised and locally advanced cases will develop PSA recurrence and metastasis over the course of the disease,[6] which will require the use of androgen deprivation therapy (ADT) alone or as part of a multimodality treatment.

This review aims to summarise the current standard of care (SoC) and available strategies in these clinical settings, as well as future therapeutic perspectives that could change treatment paradigms in the coming years.

HISTORICAL EVOLUTION OF ANDROGEN DEPRIVATION THERAPY

Mechanisms of Action and General Principles of Androgen Deprivation Therapy

In 1941, Huggins and Hodges[7] established the role of androgens, particularly testosterone, in the growth and functional processes of the prostate cell (both normal and cancerous).[5] Most androgen production occurs in the testes, and testosterone secretion is regulated by the hypothalamic-pituitary-gonadal axis. The hypothalamus produces the hypothalamic gonadotropin-releasing hormone (GnRH). This hormone stimulates the production of the luteinising hormone (LH) and the follicle-stimulating hormone (FSH) by the pituitary gland, which subsequently triggers testosterone production by testicular cells.

When androgenic stimulation is removed, both normal and cancerous prostate cells undergo apoptosis. This is why ADT has become the mainstay of systemic treatment for PCa.[8] ADT can be achieved by surgical orchiectomy or by down-regulating the production of LH and FSH with GnRH agonists (GnRHa) or antagonists. In addition, intracellular androgen synthesis can be blocked by CYP17A inhibitors, and the androgen receptor (AR) may be directly inhibited by anti-androgens (AAs).[9]

When used alone in patients with locally advanced or metastatic PCa, ADT only modestly improves survival and should therefore be considered as a palliative treatment. Extensive clinical data have established its clinical outcomes, namely the normalisation of serum PSA (associated with symptom alleviation) and tumour response in approximately 90% of patients.[10]

ADT also has a beneficial impact on quality of life (QoL), bone pain control, and complication rates of PCa.[5]

ANDROGEN DEPRIVATION THERAPY MODALITIES

Oestrogens

Prior to the development of GnRHa/antagonists, oestrogens such as diethylstilbestrol were used due to their role in GnRH secretion and androgen inactivation in order to suppress serum testosterone levels. However, this treatment modality was abandoned following studies suggesting that the effects of the treatment were equivalent to orchiectomy, but with an increased risk of heart disease and stroke.[11,12] The PATCH PR09 UK trial recently investigated whether the use of oestrogen patches could avoid the long-term complications associated with GnRHa and the thromboembolic complications associated with oral oestrogens.[13] A Phase III study is currently ongoing (Clinicaltrials.gov NCT00303784) which aims to recruit 2,150 patients.[14]

Surgical and Medical Castration

Today, ADT is achieved through surgical (bilateral orchiectomy) or medical (GnRHa or antagonists) castration. The level of serum testosterone necessary for an effective castration has long been a matter of debate.[15]

Historically, the FDA has requested that medical castration therapies lower testosterone to <0.7 nM (50 ng/dL). However, it has been suggested more recently that a lower level would be optimal. Recently, Klotz et al.[16] reviewed the results of the PR-7 study that randomly assigned patients experiencing biochemical failure after radiation therapy, or surgery plus radiation therapy to continuous or intermittent ADT.

It is worth noting that patients with first-year nadir testosterone consistently >50 ng/dL had a significantly higher risk of dying due to disease (0.7–1.7 nmol/L: hazard ratio [HR], 2.08; 95% confidence interval [CI], 1.28–3.38; >1.7 nmol/L: HR, 2.93; 95% CI, 0.70–12.30) and progressing to castration resistance (0.7–1.7 nmol/L: HR, 1.62; 95% CI, 1.20–2.18; ≥1.7 nmol/L: HR, 1.90; 95% CI, 0.77–4.70). Maximum testosterone ≥1.7 nmol/L predicted for a higher risk of dying as a result of disease (p=0.02).[16]

Bilateral Orchiectomy

Bilateral orchiectomy is an inexpensive, quick, and definitive procedure. It is irreversible and thus not applicable for (neo)adjuvant strategies and intermittent ADT. Orchiectomy has been mostly abandoned in high-income countries in favour of GnRHa as, when given the choice, more than two-thirds of men prefer an injection. In 1992, Cassileth et al.[17] asked 147 men with advanced PCa what treatment they would choose for ADT: 115 selected treatment with goserelin acetate, while only 32 chose orchiectomy.[17]

MEDICAL CASTRATION WITH GONADOTROPIN-RELEASING HORMONE AGONISTS/ANTAGONISTS

Gonadotropin-Releasing Hormone Agonists

GnRHa are long-acting synthetic GnRH analogues that have been extensively used for more than 30 years, and they are currently the main forms of ADT.[18] The current therapeutic armamentarium comprises leuprorelin (leuprolide acetate), goserelin, triptorelin, buserelin, and histrelin. The options currently available mainly include monthly, tri-monthly, 6-monthly, or yearly depot preparations of intramuscular or subcutaneous injections containing long-lasting formulations.[19-21]

As such compounds are agonists, they first stimulate the pituitary secretion of LH and FSH before down-regulating them. This causes a transient rise in the secretion of testosterone. In most patients, the testosterone surge will result in a transient increase in PSA.[22] Eventually however, in patients with a high-burden metastatic or locally advanced disease, it can potentially result in increased bone pain or urinary symptoms, acute urinary retention, and even spinal cord compression.[23]

Castration is usually achieved within 2–4 weeks.[24,25] The amplitude and duration of the testosterone surge varies according to the baseline testosterone level.[26] Pre-emptive and concomitant administration of an AA, usually a non-steroidal AA (NSAA), is thus recommended for the first 4–6 weeks of treatment with a GnRHa.

However, it should be kept in mind that the AA does not suppress the testosterone surge and only partially prevents its consequences. In one of the first leuprolide trials, flare prevention with flutamide treatment demonstrated no change or worsening of pain in 73–77% of patients, performance status in 88–90%, and alkaline phosphatase in 65%.[27]

Gonadotropin-Releasing Hormone Antagonists

In contrast to agonists, GnRH antagonists directly block the GnRH receptor without inducing an initial testosterone surge, resulting in an immediate suppression of testosterone. Degarelix is the only commercially available GnRH antagonist and is currently only available as a monthly subcutaneous injection. In the registration trial of degarelix 240/80 mg, 96% of the patients achieved a testosterone level <50 ng/dL by Day 3.[25]

In addition to the rapid onset of castration, GnRH antagonists may confer several advantages including a longer PSA progression-free survival (PFS), a more rapid effect on local symptoms, and a reduced rate of urinary infection and musculoskeletal side effects,[22,28-30] but their definitive superiority over the luteinising hormone-releasing hormone (LHRH) analogues remains to be proven.[24] The main specific side effect is 'a somewhat painful injection (moderate or mild)' reported by 40% of patients, mainly after the first injection.

ANTI-ANDROGENS

First-Generation Anti-Androgens

Cyproterone acetate (CPA) is a synthetic steroidal AA that competes with androgens at the AR level and also suppresses androgen biosynthesis, thus preventing the initial testosterone surge induced by GnRHa.[31] This is why in the past it was the preferred AA for flare prevention in Europe. Steroidal AAs are associated with loss of libido, erectile dysfunction, gynaecomastia, and cardiotoxicity associated with a risk of deep venous and arterial thromboses.

NSAAs, including flutamide, nilutamide, and bicalutamide, competitively bind to ARs. When used alone, they increase serum testosterone through a feedback mechanism. This is the reason why they are not frequently used alone. A recent Cochrane Systematic Review based on studies including 3,060 patients receiving NSAA monotherapy for advanced PCa concluded that this option was less effective than ADT in terms of overall survival (OS), clinical progression, treatment failure, and treatment discontinuation due to adverse events.

However, this review included trials with several NSAAs at various doses, including low doses that were never registered.[32] Indeed, bicalutamide, at the higher dose of 150 mg, has been extensively compared to castration in patients with locally advanced T3/T4 non-metastatic disease (M0) or metastatic disease (M1), and is registered in Europe for the treatment of patients with non-metastatic disease.[33,34]

The definitive analysis for M0 patients was performed after a median follow-up of 6.3 years.[33] In that setting, there was no difference between bicalutamide 150 mg and castration in OS (HR, 1.05; p=0.70) or time to progression (HR, 1.20; p=0.11). In contrast, there was a statistically significant

benefit in the bicalutamide monotherapy group with respect to sexual interest (p=0.029) and physical capacity (p=0.046). Bicalutamide 150 mg was well tolerated, with breast pain and gynaecomastia being the most frequent side effects. Further studies confirmed that bicalutamide 150 mg induces fewer bothersome side effects than LHRH agonists, does not decrease bone mineral density, and has less impact on lipid metabolism.[35,36]

With the development of a new generation of more potent NSAAs, there is however renewed enthusiasm for the use of these drugs as monotherapies. Tombal et al.[37] investigated the efficacy of enzalutamide monotherapy in 67 patients with advanced PCa and reported a PSA decline of ≥80% in 92.5% of the patients, with mild-to-moderate toxicity. However, NSAAs are most frequently used to prevent GnRHa-induced flare or are combined over the duration of treatment to achieve complete or maximal androgen blockade (CAB or MAB, respectively).[9]

Several meta-analyses have shown that CAB provides a significant, but limited survival advantage (2–3%) when compared with GnRHa monotherapy.[38] The Prostate Cancer Trialists' Collaborative Group (PCTCG) meta-analysis demonstrated that CAB increases 5-year OS by 1.8% (p=0.11) compared with GnRHa alone, depending on the class of AAs used. CAB with nilutamide and flutamide decreases the risk of death over castration alone by 8%, which translates into a 2.9% increase in the 5-year OS. In contrast, MAB with CPA significantly increases the risk of death by 13%, therefore reducing the 5-year OS by 2.8%.

NSAAs increase the rate of several side effects versus castration alone: diarrhoea (10% versus 2%), gastrointestinal pain (7% versus 2%), and non-specific ophthalmologic events (29% versus 5%). It is important to note that none of the meta-analyses performed so far have incorporated studies with bicalutamide 50 mg, which is the most frequently used AA due to its daily dosage and low frequency of gastrointestinal and ophthalmologic adverse effects.

Second-Generation Anti-Androgens

There are additional compounds that have been developed to target the AR pathway. These mainly aim to address current treatment gaps for progressive disease following first-line therapy of castration-resistant prostate cancers (CRPC). For example, abiraterone acetate, an androgen synthesis inhibitor; and enzalutamide, an androgen signalling pathway antagonist, are two major new agents that offer additional improvement in OS for metastatic CRPC (mCRPC) patients.[39-46]

CONTEMPORARY INDICATIONS OF ANDROGEN DEPRIVATION THERAPY IN ADVANCED PROSTATE CANCER

Although hormone therapy (HT) is the mainstay of systemic therapy in PCa, its indications are still poorly recognised by many urologists outside the context of a symptomatic patient with metastatic PCa. Indeed, the answers to a simple question on the evidence provided in the literature are not unanimous regarding the appropriate timing and duration of ADT.

Metastatic Patients

Patients who initially present with disseminated disease should receive immediate ADT for surgical castration, GnRHa and a short course of AA, or GnRH antagonists. In the recently published early results of the STAMPEDE (Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy) trial, 8,000 newly diagnosed PCa patients received ADT (control arm) or experimental therapy. Nine-hundred-and-seventeen M1 PCa patients were included in the control arm and the results were published at a median follow-up of 20 months.[47] The median OS was 42 months. However, the extremely broad interquartile range (IQR) of 22.7–90.7 months suggested a very heterogeneous response to ADT.

The initial response to ADT is fairly short but very heterogeneous, with a median IQR failure-free survival of 11.2 (range: 5.1–28.8) months. This means that men diagnosed with metastatic PCa will spend three-quarters of their life in the CRPC state, receiving multiple lines of therapies.

Primary Androgen Deprivation Therapy in Non-Metastatic Patients

Many asymptomatic men receive primary ADT for localised PCa (T1-2, N0 [No regional lymph node involvement], M0) to avoid or postpone radical therapy. In 2005, Shahinian et al.[48] assessed 100,274 PCa patients from the SEER registry and reported a consistent increase in GnRHa use by year for all ages, stages, and grades from 1991–1999. Even in men ≥80 years with localised stage and low-to-moderate grade tumours, primary GnRHa use

increased over the study period. The Early Prostate Cancer trial, which included 8,113 men with M0 PCa and aimed to assess the efficacy of early treatment with bicalutamide, clearly demonstrated that there is no long-term benefit to the use of this treatment.

After a median follow-up of 7.4 years, there was a clear trend (HR, 1.16; p=0.07) towards shortened survival in patients with localised disease treated with immediate HT.[49] More recently, Potosky et al.[50] conducted a retrospective cohort study on 15,170 men diagnosed with localised PCa between 1995 and 2008 who were treated with primary ADT. Primary ADT was associated with neither a risk of all-cause mortality nor PCa-specific mortality, except among the subgroup of men with a high-risk of PCa progression.

Similarly, ADT has become the SoC for most men with an isolated rise in PSA after radical treatment. Interestingly, there is no evidence to support such immediate treatment. Instead, it has been suggested that this treatment line may only benefit a minority of patients while hurting a majority by exposing them to long-term side effects.

Two large series have retrospectively investigated the potential benefit of an immediate treatment. Moul et al.[51] reviewed a database of 4,967 patients treated by radical prostatectomy (RP), 1,352 of whom had a PSA recurrence. In the overall cohort, early ADT did not have an impact on clinical metastases. Early ADT was associated with delayed clinical metastasis only in patients with a Gleason score of >7 or a PSA doubling time of ≤12 months. Race, age at RP, and PSA at diagnosis had no effect on metastasis-free survival (p>0.05). This was recently confirmed by Garcia-Albeniz et al.[52] in a retrospective review of 2,096 patients treated with RP or radiotherapy. The adjusted mortality HR for immediate versus deferred ADT was 0.91 (95% CI, 0.52–1.60), which translated into a similar 5-year OS (difference between groups: -2.0%; 95% CI, -10.0–5.9%).

The same paradigm also applies to locally advanced PCa for which radical treatment is denied. The EORTC trial 30891 clearly suggests that ADT can be safely postponed in many patients with locally advanced PCa (T1-2, N+, M0, or T3-4, Nx, M0) who are not eligible for radical treatment. This trial, which randomised 985 patients to receive immediate ADT versus deferred ADT at symptomatic disease progression, reported a modest increase in OS in the case of immediate ADT (HR, 1.25; p>0.1) as a result of fewer non-PCa related deaths. Notably, the time from randomisation to CRPC did not differ significantly. More importantly, the median time to start deferred treatment was 7 years, and 26% of patients in the delayed ADT group died without ever receiving treatment.[53] Additional analysis of this EORTC trial suggest that only men with PSA level >50 ng/mL or with PSA doubling time <12 months are at risk of progression.[54]

Taken together, these data suggest that in many patients with asymptomatic locally advanced PCa, HT can be delayed, thus avoiding the adverse effects associated with long-term treatment. Careful selection of patients based on age, PSA kinetics, imaging, and Gleason score could aid in the identification of patients who would most benefit from HT.

Androgen Deprivation Therapy as Adjuvant to Local Therapies

In contrast to its limited benefits as a primary therapy, ADT has gained a major role in the adjuvant setting, in addition to radical therapies. Here it has been shown to significantly increase OS, especially in conjunction with radiotherapy. The only randomised trial showing a substantial advantage for immediate ADT after surgery is the ECOG trial, which compared immediate versus deferred ADT in patients with positive lymph nodes who underwent RP and pelvic lymph node dissection.[55] At follow-up (median of 11.9 years), immediate ADT significantly improved OS (HR, 1.84; p=0.04) and PCa-specific survival (HR, 4.09; p=0.0004). However, the patients in this study had higher tumour burden (e.g. seminal vesicle involvement, positive surgical margins, Gleason score of 8–10) than most contemporary patients, and recent RP series suggest that not all patients with a positive lymph node dissection require immediate HT.[56]

The benefit of ADT in combination with external beam radiation therapy (EBRT) has been extensively studied. In the EORTC 22863 trial, it was shown that 3 years of treatment with an adjuvant LHRH agonist in EBRT patients with locally advanced PCa, decreased the risk of death by 49% versus EBRT alone.[57] In the RTOG 85-31 trial, lifelong administration of an LHRH agonist decreased the risk of death by 23% versus EBRT alone.[58] The optimal duration of adjuvant ADT for

locally advanced PCa is still unclear. The EORTC 22961 trial compared 6 months with 3 years of (neo)adjuvant ADT in 1,113 patients with locally advanced PCa treated with EBRT. A slight OS benefit in favour of long-term ADT was demonstrated.[59] In the trial, 5-year overall mortality for short-term and long-term suppression was 19.0% and 15.2%, respectively; the observed HR was 1.42. The benefit of extending the duration of ADT beyond 6 months should therefore be discussed with the patient as regards to the long-term toxicity of ADT.

A shorter adjuvant HT treatment is also beneficial for patients with high-risk localised PCa (i.e. Gleason score >7 or PSA >20 ng/mL or Stage T2c) who are primarily treated with EBRT. In a trial conducted by D'Amico et al.,[60] 206 patients were randomised to receive EBRT alone or combined with HT administered over 6 months. After a median follow-up of 4.5 years, the ADT/EBRT combination was associated with a longer time to PSA recurrence (HR, 0.22; p<0.001), PCa-specific mortality (HR, 0.23; p=0.005), and all-cause mortality (HR, 0.30; p<0.001).

Intermittent Androgen Deprivation Therapy

The rationale for using intermittent androgen deprivation (IAD) therapy has arisen from studies conducted in an animal model of Shionogi mammary carcinoma in the early 1990s. These studies suggest that IAD prolongs the duration of androgen dependence.[61] This generated the hypothesis that IAD would delay the onset of CRPC and its associated complications, which are both debilitating and deadly.

Several trials have investigated the role of IAD, including four large Phase III randomised trials, from which core evidence has been produced. The South European Uroncological Group (SEUG) trial enrolled 766 patients with locally advanced or metastatic PCa.[62] FinnProstate Study VII enrolled 852 locally advanced or metastatic patients.[63] The NCIC Clinical Trials Group enrolled 1,386 patients with a PSA level >3 ng/mL more than 1 year after primary or salvage radiotherapy for localised PCa.[64] Finally, The SWOG trial 9346, randomised 3,040 metastatic PCa patients.

Several meta-analyses and systemic reviews have been conducted, and generally discussed the equivalence of IAD versus continuous ADT. In a systematic review by Niraula et al.,[65] nine studies with 5,508 patients met criteria for inclusion. There were no significant differences in time-to-event outcomes between the groups in the studies. The pooled HR for OS was 1.02 (95% CI, 0.94–1.11) for IAD compared with CAD, and the HR for PFS was 0.96 (95% CI, 0.76–1.20). More PCa-related deaths with IAD were balanced by more deaths not related to PCa with CAD. Superiority of IAD for sexual function, physical activity, and general wellbeing was observed in some trials. Median cost savings with IAD were estimated to be 48%.

However, some important facts should be mentioned about IAD. Firstly, the Phase III trials were based on a conditional randomisation methodology, thus only including patients who had experienced a major PSA decrease. Secondly, most of the trials reported an increase in PCa-related deaths with IAD that is to be balanced by more deaths not related to PCa with continuous ADT.[65] Thirdly, although some trials report a benefit in QoL, it is important to mention that none of these trials used a placebo control, and compared men in whom treatment was suspended: men left with the disappointment of having to prolong ADT. This is important, considering that the recovery of normal testosterone is unpredictable and usually slow when agonists are suspended.[66]

Finally, the role of ADT in M1 PCa patients is still controversial, considering the results of SWOG 9346.[67] The study was designed to show that IAD was not inferior to CAD in terms of OS post-randomisation. In total, 3,040 metastatic PCa patients were recruited, but after 7 months of CAB, only 1,535 patients had achieved a PSA of ≤4.0 ng/mL and were randomised. The median and 10-year OS rates from randomisation were 5.8 years and 29% for CAD, and 5.1 years and 23% for IAD. Therefore the studies failed to prove that IAD was non-inferior to CAD (HR, 1.09; 95% CI, 0.95–1.24). Patients were stratified by disease extent using a definition of minimal disease (spine, pelvis bone metastases, and/or lymph nodes) versus extensive disease (>4 bone metastases with at least 1 beyond pelvis and vertebral column, and/or visceral disease [lung or liver]). The median OS of patients with extensive disease patients was 4.9 years for IAD and 4.4 years for CAD; in patients with minimal disease, median OS was 5.4 years for IAD and 6.9 years for CAD.

THE ROLE OF HORMONE THERAPY IN THE TREATMENT OF CASTRATION-RESISTANT PROSTATE CANCER

After initial response to ADT therapy, most patients with advanced or metastatic PCa will eventually progress to CRPC, defined by several rises in PSA or by clinical or radiological progression of disease (based on RECIST criteria).[68]

In the last 10 years, it has been demonstrated that most patients progressed in a low testosterone environment through reactivation of AR pathways. Several mechanisms have been involved, including two that can be addressed with modern drugs. Taxane-based chemotherapy with docetaxel plus prednisone was established as the SoC for first-line therapy in CRPC[69,70] after two Phase III trials demonstrated the benefits of docetaxel and prednisone on OS, 3-year survival, and PSA response rates, compared with mitoxantrone and prednisone.[71,72] This has been the SoC since 2004, but the scenario has changed with the arrival of novel HTs into the clinic.

Switching Gonadotropin-Releasing Hormone Agonists at the Time of Castration-Resistant Prostate Cancer Progression

The late reactivation of the AR-underlying CRPC may arise from GnRHa losing their efficacy over time, with the consequence that testosterone increases above the castration level, a phenomenon known as testosterone breakthrough.[73] In a retrospective study by Morote et al.,[74] PSA PFS was 88 and 137 months, respectively, in patients with or without testosterone breakthroughs >32 ng/dL ($p<0.03$).

Lawrentschuk et al.[75] investigated the benefit of re-challenging 39 CRPC patients with a different GNRHa. Sixty-nine percent of the patients experienced a PSA decrease, and the median PSA decrease was 69.3% in patients switching from leuprolide to goserelin, and 6.4% in patients switching from goserelin to leuprolide.[75] Practically, this stresses the importance of measuring each patient's testosterone levels in case of CRPC progression and eventually adapting therapy to optimise testosterone control.

Role of First-Generation Hormonal Therapies in the Management of Castration-Resistant Prostate Cancer Progression

In the absence of curative second-line treatment, most physicians have historically prescribed various AAs such as bicalutamide, flutamide, or nilutamide; adrenal synthesis inhibitors such as ketoconazole or aminoglutethimide; oestrogens and derivatives, or steroids including prednisone, prednisolone, hydrocortisone, or dexamethasone.

These drugs have mostly been tested in small Phase II trials with PSA response and PFS as the main endpoints. These trials were extensively reviewed by Tombal in 2012.[76] Overall, a PSA response decrease of >50% was observed in 25–65% of patients for durations of 3–6 months. With the exception of low-dose bicalutamide, none of these agents have been compared with modern AR pathway inhibitors such as abiraterone and enzalutamide. The TERRAIN trial compared bicalutamide 50 mg with enzalutamide 160 mg in 375 asymptomatic or mildly symptomatic mCRPC patients prior to chemotherapy.[77] Median PFS was 15.7 months in the enzalutamide arm compared with 5.8 months in the bicalutamide arm (HR, 0.44; 95% CI, 0.34–0.57; $p<0.0001$). Serious adverse events were experienced by 31.1% and 23.3% of patients treated with enzalutamide or bicalutamide, respectively.[77]

The remaining role of these agents in the modern era was discussed during the recent St Gallen Advanced Prostate Cancer Consensus Conference (APCCC) in 2015.[78] A majority (52%) of the panellists felt that these older agents are not appropriate treatment options for a patient who is not considered a candidate for chemotherapy, where abiraterone and enzalutamide are available and reimbursed. Nevertheless, 32% of the panellists would still recommend them in a minority of select patients and 16% suggested that they would recommend these agents in a majority of patients. However, all panel members considered it appropriate to use these first-generation AAs, if abiraterone and enzalutamide are unavailable.

MODERN ANDROGEN RECEPTOR PATHWAY INHIBITORS

Abiraterone

Abiraterone acetate is a CYP17A (α-hydroxylase) enzyme inhibitor and thus an androgen biosynthesis inhibitor. In CRPC patients, it primarily acts to inhibit the synthesis of androgens at the adrenal level and in PCa cells that upregulate CYP14A. Through a feedback mechanism, it increases adrenocorticotropic hormone and generates a mineralocorticoid excess, potentially

causing side effects such as hypertension, hypokalaemia, and lower-limb oedema. When administered with prednisone 5 mg twice daily, it shows an excellent tolerability profile. Abiraterone is also converted to a more active compound D4A with dual function: a steroidogenic enzyme blocker and a potent AR antagonist, and thus may have more than one mechanism of action.[79]

Abiraterone/prednisone has demonstrated improved OS in both docetaxel-naïve and docetaxel-treated patients in key Phase III trials.[42,45,80,81] In the first Phase III study in 1,195 docetaxel-treated mCRPC patients (COU-AA-301),[42,43,80] OS with abiraterone and prednisone was improved over placebo and prednisone (median 15.8 months versus 11.2 months; HR, 0.74; 95% CI, 0.64–0.86). Statistically significant outcomes were also reported for time to PSA progression and PFS.

Similar results were observed in asymptomatic or mildly symptomatic chemotherapy-naïve patients with no visceral metastases, particularly in a Phase III trial of 1,088 CRPC patients who were randomised to either abiraterone plus prednisone or placebo plus prednisone (COU-AA-302).[44,81] In the study, Abiraterone and prednisone doubled the time to radiological progression-free survival (rPFS) compared with placebo and prednisone (HR,0.52; 95% CI, 0.45-0.61), p<0.0001).[44] After a median follow-up of 49.2 months, OS was significantly higher in the abiraterone arm (median 34.7 months versus 30.3 months; HR, 0.81; 95% CI, 0.70–0.93).[39,45] Abiraterone treatment effect was more pronounced when adjusting for the 44% of placebo prednisone patients who subsequently received abiraterone (HR=0.74). After a median follow-up of 49.2 months, OS was significantly higher in the abiraterone arm (median 34.7 months versus 30.3 months; HR, 0.81; 95% CI, 0.70-0.93).[39,45]

In these patients, clinically significant endpoints in the COU-AA-302 trial, and early use of abiraterone and prednisone in asymptomatic or mildly symptomatic patients, are the delay in the time to chemotherapy by 8.4 months, median time to progression of worse pain intensity by 7.3 months, and median time to functional status deterioration (FACT-P total score) by 4.4 months.

Enzalutamide

Enzalutamide is an AR-signalling inhibitor that targets multiple steps in the AR signalling pathway.[82] It blocks androgen binding to AR, prevents nuclear translocation of AR, and impairs AR binding to DNA, thus preventing modulation of gene expression.[82,83] Enzalutamide is an AR antagonist with higher AR affinity than bicalutamide in cells overexpressing the AR.[82]

The AFFIRM trial randomised 1,199 patients post-docetaxel between enzalutamide and placebo.[41,46] After a median follow-up of 14.4 months, improved outcomes were observed in the enzalutamide group versus placebo, both in terms of median survival (18.4 months versus 13.6 months) and PSA response, as well as PFS and QoL.

In the Phase III PREVAIL study,[40] which aimed to evaluate the efficacy and safety of enzalutamide in 1,717 mCRPC patients who were asymptomatic or mildly symptomatic and chemotherapy-naïve, median OS (HR=0.71; p<0.0001) was significantly higher in the enzalutamide arm compared with placebo. Enzalutamide reduced the risk of radiographic progression by 81% (HR, 0.19; 95% CI, 0.15–0.23; p<0.001). This trial differed from the COU-AA-302 trial in that there was no prednisone in either the active or placebo arm, and patients with visceral metastases (lung or liver metastases) were permitted into the study. The trial led to the extension of the indication in chemotherapy-naïve patients by the European Medicines Agency (EMA) in October 2014.[84]

Similar to COU-AA-302, the PREVAIL trial was highly remarkable for its secondary endpoints. Indeed, enzalutamide delayed the time to chemotherapy by 17.2 months, median time until decline in relation to the FACT-P global score by 5.7 months, and time to pain progression (by FACT-P) by 5.5 months.[85]

FUTURE OUTLOOK ON ANDROGEN DEPRIVATION THERAPY

Early Combination of Androgen Deprivation Therapy with Docetaxel

ADT may be given with upfront docetaxel chemotherapy in patients presenting with metastatic hormone-sensitive disease, particularly those with high volume disease (HVD), defined as: presence of visceral metastases or four bone lesions, where at least one of them is outside the axial skeleton.

In the CHAARTED trial, 790 men with such criteria (65% of whom had HVD) received ADT plus six cycles of docetaxel without prednisone as a

first-line treatment compared with ADT alone.[86,87] After a median follow-up of 29 months, OS was significantly improved over ADT alone (58 versus 44 months, respectively). Most notable were the results observed in patients from the HVD subgroup. A median difference in OS of 17 months (49 versus 32 months) was observed.

This study differs from what was found in the French GETUG-15 trial,[86] which primarily contained a lower-risk patient group (only 21% in high-risk Glass group). Clinical PFS and biochemical PFS were significantly improved but no OS difference was seen with the addition of up to nine cycles of docetaxel chemotherapy.

At ASCO GU 2015, updated results of the GETUG-15 trial were presented with a longer follow-up of about 80 months. These results showed that the median OS was 46.5 months in the ADT arm and 60.9 months in the ADT with docetaxel arm (HR, 0.9; 95% CI, 0.7–1.2). In a retrospective analysis, which used the same definition of HVD as the CHAARTED trial discussed below, the subgroup of patients with HVD showed a median OS of 35.1 months in the ADT alone arm, compared with 39 months in the ADT plus chemotherapy arm (HR, 0.8; 95% CI, 0.6–1.2). The outcomes in HVD patients were similar to those in the CHAARTED trial, however the trial showed a non-significant improvement in OS with ADT with docetaxel of about 4 months.[88,89]

Additional data have come from the ongoing STAMPEDE trial, which is also evaluating the role of ADT plus docetaxel therapy in patients with locally advanced and metastatic disease.[90] The first OS results were presented at the ASCO meeting in June 2015.[47,91] Data from 2,962 hormone-naïve men from four of the study's nine arms revealed that after a median follow-up of 42 months, median OS was 77 months in the SoC plus docetaxel arm versus 67 months in the SoC arm alone. This translated into a 24% reduction in the risk of death associated with docetaxel chemotherapy and ADT (HR, 0.76; 95% CI, 0.63-0.91). The results are most remarkable in metastatic patients as opposed to the M0 population. In the metastatic PCa patient subpopulation, there was a 22-month difference in OS (65 versus 43 months) between both arms, respectively.

Vale et al.[92] have conducted a systematic review of these three trials and have shown that the addition of docetaxel to SoC improves 4-year survival by 9% (95% CI, 5-14; HR, 0.77; 95% CI, 0.68-0.87; p<0.0001).[92]

Neoadjuvant Therapy and Rising Prostate-Specific Antigen: Combinations with Novel Anti-Androgens

Few clinical data are currently available to determine whether additional clinical benefit can be obtained by combining GnRHa with second-generation AAs in the neoadjuvant setting. In a Phase II randomised neoadjuvant study, 58 patients with high-risk PCa received intense ADT with leuprolide plus abiraterone. The combination seemed more effective than leuprolide alone, as intratumoural androgen levels were significantly lower in the combination group for a higher total pathological response (34% versus 15%).[93]

A Phase II study is currently recruiting patients to evaluate 'enzalutamide plus leuprolide' versus 'enzalutamide plus leuprolide, abiraterone, and prednisone' as neoadjuvant therapy for high-risk PCa patients undergoing prostatectomy.[94] A Phase III, randomised efficacy and safety study will soon begin recruitment to evaluate 'enzalutamide plus leuprolide, enzalutamide monotherapy', and 'placebo plus leuprolide' in men with high-risk non-metastatic PCa progressing after definitive therapy.[95] Other novel agents such as ARN-509 are also being evaluated in combination with abiraterone.[96]

Adverse Events and Quality of Life of Patients Undergoing Androgen Deprivation Therapy

ADT remains the cornerstone of advanced PCa treatment, and is now used as a neoadjuvant or adjuvant therapy with radiotherapy in earlier stages. Adverse events and reduced QoL in men undergoing ADT must be considered before widening selection criteria for ADT use in PCa patients, especially since many PCa patients are aged 65 years and above, and may present with several comorbidities. Numerous adverse events have been reported with ADT: hot flushes, loss of libido, sexual dysfunction, gynaecomastia, decrease in bone mineral density, increase in fat mass associated with loss of lean muscle mass, metabolic syndrome, diabetes, and increased risk of myocardial infarction and cardiovascular disease in general.[97-101]

Short and long-term ADT can be associated with impaired QoL, including decreased short-term mental, cognitive, and emotional well-being, as well

as physical symptoms. Patients often self-report memory loss, depressive symptoms, insomnia or sleep disturbances, difficulty in concentrating, and nervousness.[102-105] The physical impact of ADT comprises bone density changes and fractures, loss of muscle strength, and fatigue. A third cluster of symptoms comprises relationship and affective symptoms, often triggered by gynaecomastia and functional changes in sexuality and sexual organs.[106-109] Amongst the measures that can alleviate the side effects of ADT, supervised resistance training exercise is expected to play a major role. Several trials have examined whether various exercise strategies can counteract the metabolic effects of ADT.[110]

Cost-Effectiveness of Androgen Deprivation Therapy in Advanced Prostate Cancer

In a meta-analysis published in 2000, the cost-effectiveness of ADT was evaluated in advanced PCa. Orchiectomy was established as the most cost-effective ADT modality, while CAB was the least economically effective option.[111] While the combination of ADT with docetaxel or novel AAs may generate higher costs, some GnRHa have generic formulations that are already on the market, which could help to improve the cost-efficacy of the management of advanced PCa, lower overall costs, and increase patient access to therapy.

CONCLUSION

ADT in advanced PCa has gone through considerable evolution, but still remains a cornerstone of the therapeutic armamentarium in the treatment of PCa. Its contemporary role in advanced PCa, particularly with second-generation AAs, has emerged as a therapeutic modality in select settings for both castration-sensitive and castration-resistant advanced PCa. ADT in combination with novel hormonal agents is now being explored in the neoadjuvant setting, and chemotherapy in combination with ADT must be seriously considered in selected patients after the results of recent randomised trials. Upcoming clinical data will help to further refine risk stratification and optimal strategies in advanced PCa, particularly in light of benefit-to-risk ratios, QoL, and pharmacoeconomic considerations.

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REFERENCES

1. Ferlay J et al; International Agency for Research on Cancer. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11. 2013. Available at: http://globocan.iarc.fr. Last accessed: 12 January 2016.

2. Arnold M et al. Recent trends in incidence of five common cancers in 26 European countries since 1988: Analysis of the European Cancer Observatory. Eur J Cancer. 2015;51(9):1164-87.

3. De Angelis R et al. Cancer survival in Europe 1999-2007 by country and age: results of EUROCARE--5-a population-based study. Lancet Oncol. 2014;15(1): 23-34.

4. Pokorny MR, Scott DJ. Do Maori and Pacific Islander men present with more advanced prostate cancer than European New Zealand men? An analysis of 486 men undergoing biopsy in Auckland. BJU international. 2011;107 Suppl 3:27-32.

5. Yap TA et al. The changing therapeutic landscape of castration-resistant prostate cancer. Nat Rev Clin Oncol. 2011;8(10): 597-610.

6. Beltran H et al. New therapies for castration-resistant prostate cancer: efficacy and safety. Eur Urol. 2011;60(2):279-90.

7. Huggins C, Hodges CV. Studies on prostatic cancer. I. The effect of castration, of estrogen and androgen injection on serum phosphatases in metastatic carcinoma of the prostate. CA Cancer J Clin. 1972;22(4):232-40.

8. Sharifi N et al. Androgen deprivation therapy for prostate cancer. JAMA. 2005;294(2):238-44.

9. Loblaw DA et al; American Society of Clinical Oncology. Initial hormonal management of androgen-sensitive metastatic, recurrent, or progressive prostate cancer: 2006 update of an American Society of Clinical Oncology practice guideline. J Clin Oncol. 2007;25(12):1596-605.

10. Dai B et al. Kinetics of testosterone recovery in clinically localized prostate cancer patients treated with radical prostatectomy and subsequent short-term adjuvant androgen deprivation therapy. Asian J Androl. 2013;15(4): 466-70.

11. Byar DP. Proceedings: The Veterans Administration Cooperative Urological Research Group's studies of cancer of the prostate. Cancer.1973;32(5):1126-30.

12. Byar DP, Corle DK. Hormone therapy for prostate cancer: results of the Veterans Administration Cooperative Urological Research Group studies. NCI Monogr. 1988;(7):165-70.

13. Langley RE et al. Cardiovascular outcomes in patients with locally advanced and metastatic prostate cancer treated with luteinising-hormone-releasing-hormone agonists or transdermal oestrogen: the randomised, phase 2 MRC PATCH trial (PR09). Lancet Oncol. 2013;14(4):306-16.

14. National Cancer Institute; Imperial College London. Hormone Therapy in Treating Patients With Locally Advanced or Metastatic Prostate Cancer.

NCT00303784. https://clinicaltrials.gov/ct2/show/NCT00303784.

15. Djavan B et al. Testosterone in prostate cancer: the Bethesda consensus. BJU Int. 2012;110(3):344-52.

16. Klotz L et al. Nadir testosterone within first year of androgen-deprivation therapy (ADT) predicts for time to castration-resistant progression: a secondary analysis of the PR-7 trial of intermittent versus continuous ADT. J Clin Oncol. 2015;33(10):1151-6.

17. Cassileth BR et al. Quality of life and psychosocial status in stage D prostate cancer. Zoladex Prostate Cancer Study Group. Qual Life Res. 1992;1(5):323-9.

18. Tolis G et al. Tumor growth inhibition in patients with prostatic carcinoma treated with luteinizing hormone-releasing hormone agonists. Proc Natl Acad Sci U S A. 1982;79(5):1658-62.

19. Fowler JE et al. Evaluation of an implant that delivers leuprolide for 1 year for the palliative treatment of prostate cancer. Urology. 2000;55(5):639-42.

20. Fowler JE et al. Safety and efficacy of an implantable leuprolide delivery system in patients with advanced prostate cancer. J Urol. 2000;164(3 Pt 1):730-4.

21. Geiges G et al. Clinical development of two innovative pharmaceutical forms of leuprorelin acetate. Ther Adv Urol. 2013;5(1):3-10.

22. Tombal B et al. Additional analysis of the secondary end point of biochemical recurrence rate in a phase 3 trial (CS21) comparing degarelix 80 mg versus leuprolide in prostate cancer patients segmented by baseline characteristics. Eur Urol. 2010;57(5):836-42.

23. Waxman J et al. Importance of early tumour exacerbation in patients treated with long acting analogues of gonadotrophin releasing hormone for advanced prostatic cancer. Br Med J. 1985;291(6506):1387-8.

24. Mottet N et al. EAU Guidelines on Prostate Cancer 2015. 2015. Accessible at: http://uroweb.org/guideline/prostate-cancer/. Last accessed: 30 November 2015.

25. Van Poppel H et al. Degarelix: a novel gonadotropin-releasing hormone (GnRH) receptor blocker--results from a 1-yr, multicentre, randomised, phase 2 dosage-finding study in the treatment of prostate cancer. Eur Urol. 2008;54(4):805-13.

26. Damber JE et al. The effect of baseline testosterone on the efficacy of degarelix and leuprolide: further insights from a 12-month, comparative, phase III study in prostate cancer patients. Urology. 2012;80(1):174-80.

27. Crawford ED et al. A controlled trial of leuprolide with and without flutamide in prostatic carcinoma. N Engl J Med. 1989;321(7):419-24.

28. Klotz L et al. Disease control outcomes from analysis of pooled individual patient data from five comparative randomised clinical trials of degarelix versus luteinising hormone-releasing hormone agonists. Eur Urol. 2014;66(6):1101-8.

29. Albertsen PC et al. Cardiovascular morbidity associated with gonadotropin releasing hormone agonists and an antagonist. Eur Urol. 2014;65(3):565-73.

30. Axcrona K et al. Androgen deprivation therapy for volume reduction, lower urinary tract symptom relief and quality of life improvement in patients with prostate cancer: degarelix vs goserelin plus bicalutamide. BJU Int. 2012;110(11):1721-8.

31. Sugiono M et al. Bicalutamide vs cyproterone acetate in preventing flare with LHRH analogue therapy for prostate cancer--a pilot study. Prostate Cancer Prostatic Dis. 2005;8(1):91-4.

32. Kunath F et al. Non-steroidal antiandrogen monotherapy compared with luteinising hormone-releasing hormone agonists or surgical castration monotherapy for advanced prostate cancer. Cochrane Database Syst Rev. 2014;6:CD009266.

33. Iversen P et al. Bicalutamide monotherapy compared with castration in patients with nonmetastatic locally advanced prostate cancer: 6.3 years of followup. J Urol. 2000;164(5):1579-82.

34. Iversen P et al. Casodex (bicalutamide) 150-mg monotherapy compared with castration in patients with previously untreated nonmetastatic prostate cancer: results from two multicenter randomized trials at a median follow-up of 4 years. Urology. 1998;51(3):389-96.

35. Smith MR et al. Cross-sectional study of bone turnover during bicalutamide monotherapy for prostate cancer. Urology. 2003;61(1):127-31.

36. Smith MR et al. Bicalutamide monotherapy versus leuprolide monotherapy for prostate cancer: effects on bone mineral density and body composition. J Clin Onc. 2004;22(13):2546-53.

37. Tombal B et al. Enzalutamide monotherapy in hormone-naive prostate cancer: primary analysis of an open-label, single-arm, phase 2 study. Lancet Oncol. 2014;15(6):592-600.

38. Maximum androgen blockade in advanced prostate cancer: an overview of the randomised trials. Prostate Cancer Trialists' Collaborative Group. Lancet. 2000;355(9214):1491-8.

39. Ryan CJ et al. Final overall survival (OS) analysis of COU-AA-302, a randomized phase 3 study of abiraterone acetate (AA) in metastatic castration-resistant prostate cancer (mCRPC) patients (pts) without prior chemotherapy. Abstract 753O. 2014 European Society of Medical Oncology (ESMO) meeting, Madrid, Spain, 26-30 September 2014.

40. Beer TM, Tombal B. Enzalutamide in metastatic prostate cancer before chemotherapy. N Engl J Med. 2014;371(18):1755-6.

41. Fizazi K et al. Effect of enzalutamide on time to first skeletal-related event, pain, and quality of life in men with castration-resistant prostate cancer: results from the randomised, phase 3 AFFIRM trial. Lancet Oncol. 2014;15(10):1147-56.

42. Fizazi K et al. Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncol. 2012;13(10):983-92.

43. Logothetis CJ et al. Effect of abiraterone acetate and prednisone compared with placebo and prednisone on pain control and skeletal-related events in patients with metastatic castration-resistant prostate cancer: exploratory analysis of data from the COU-AA-301 randomised trial. Lancet Oncol. 2012;13(12):1210-7.

44. Rathkopf DE et al. Updated Interim Efficacy Analysis and Long-term Safety of Abiraterone Acetate in Metastatic Castration-resistant Prostate Cancer Patients Without Prior Chemotherapy (COU-AA-302). Eur Urol. 2014;66(5):815-25.

45. Ryan CJ et al. Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naive men with metastatic castration-resistant prostate cancer (COU-AA-302): final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncol. 2015;16(2):152-60.

46. Scher HI et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med. 2012;367(13):1187-97.

47. James ND et al. Survival with Newly Diagnosed Metastatic Prostate Cancer in the "Docetaxel Era": Data from 917 Patients in the Control Arm of the STAMPEDE Trial (MRC PR08, CRUK/06/019). Eur Urol. 2015;67(6):1028-38.

48. Shahinian VB et al. Increasing use of gonadotropin-releasing hormone agonists for the treatment of localized prostate carcinoma. Cancer. 2005;103(8):1615-24.

49. McLeod DG et al. Bicalutamide 150 mg plus standard care vs standard care alone for early prostate cancer. BJU Int. 2006;97(2):247-54.

50. Potosky AL et al. Effectiveness of primary androgen-deprivation therapy for clinically localized prostate cancer. J Clin Oncol. 2014;32(13):1324-30.

51. Moul JW et al. Early versus delayed

hormonal therapy for prostate specific antigen only recurrence of prostate cancer after radical prostatectomy. J Urol. 2004;171(3):1141-7.

52. Garcia-Albeniz X et al. Immediate versus deferred initiation of androgen deprivation therapy in prostate cancer patients with PSA-only relapse. An observational follow-up study. Eur J Cancer. 2015;51(7):817-24.

53. Studer UE et al. Differences in time to disease progression do not predict for cancer-specific survival in patients receiving immediate or deferred androgen-deprivation therapy for prostate cancer: final results of EORTC randomized trial 30891 with 12 years of follow-up. Eur Urol. 2014;66(5):829-38.

54. Studer UE et al. Using PSA to guide timing of androgen deprivation in patients with T0-4 N0-2 M0 prostate cancer not suitable for local curative treatment (EORTC 30891). Eur Urol. 2008;53(5): 941-9.

55. Messing EM et al. Immediate versus deferred androgen deprivation treatment in patients with node-positive prostate cancer after radical prostatectomy and pelvic lymphadenectomy. Lancet Oncol. 2006;7(6):472-9.

56. Briganti A et al. Two positive nodes represent a significant cut-off value for cancer specific survival in patients with node positive prostate cancer. A new proposal based on a two-institution experience on 703 consecutive N+ patients treated with radical prostatectomy, extended pelvic lymph node dissection and adjuvant therapy. Eur Urol. 2009;55(2):261-70.

57. Bolla M et al. Long-term results with immediate androgen suppression and external irradiation in patients with locally advanced prostate cancer (an EORTC study): a phase III randomised trial. Lancet. 2002;360(9327):103-6.

58. Pilepich MV et al. Androgen suppression adjuvant to definitive radiotherapy in prostate carcinoma--long-term results of phase III RTOG 85-31. Int J Radiat Oncol Biol Phys. 2005;61(5): 1285-90.

59. Bolla M et al. Duration of androgen suppression in the treatment of prostate cancer. N Engl J Med. 2009;360(24): 2516-27.

60. D'Amico AV et al. Six-month androgen suppression plus radiation therapy compared with radiation therapy alone for men with prostate cancer and a rapidly increasing pretreatment prostate-specific antigen level. J Clin Oncol. 2006;24(25):4190-5.

61. Akakura K et al. Effects of intermittent androgen suppression on androgen-dependent tumors. Apoptosis and serum prostate-specific antigen. Cancer. 1993;71(9):2782-90.

62. Calais da Silva FE et al. Intermittent androgen deprivation for locally advanced and metastatic prostate cancer: results from a randomised phase 3 study of the South European Uroncological Group. Eur Urol. 2009;55(6):1269-77.

63. Salonen AJ et al. The FinnProstate Study VII: intermittent versus continuous androgen deprivation in patients with advanced prostate cancer. J Urol. 2012;187(6):2074-81.

64. Crook JM et al. Intermittent androgen suppression for rising PSA level after radiotherapy. N Engl J Med. 2012;367(10):895-903.

65. Niraula S et al. Treatment of prostate cancer with intermittent versus continuous androgen deprivation: a systematic review of randomized trials. J Clin Oncol. 2013;31(16):2029-36.

66. Kaku H et al. Time course of serum testosterone and luteinizing hormone levels after cessation of long-term luteinizing hormone-releasing hormone agonist treatment in patients with prostate cancer. Prostate. 2006;66(4):439-44.

67. Hussain M et al. Intermittent versus continuous androgen deprivation in prostate cancer. N Engl J Med. 2013;368(14):1314-25.

68. Fitzpatrick JM et al. Optimal management of metastatic castration-resistant prostate cancer: highlights from a European Expert Consensus Panel. Eur J Cancer. 2014;50(9):1617-27.

69. Heidenreich A et al; European Association of Urology. EAU guidelines on prostate cancer. Part II: Treatment of advanced, relapsing, and castration-resistant prostate cancer. Eur Urol. 2014;65(2):467-79.

70. Basch E et al. Systemic therapy in men with metastatic castration-resistant prostate cancer: American Society of Clinical Oncology and Cancer Care Ontario clinical practice guideline. J Clin Oncol. 2014;32(30):3436-48.

71. Petrylak DP et al. Evaluation of prostate-specific antigen declines for surrogacy in patients treated on SWOG 99-16. J Natl Cancer Inst. 2006;98(8): 516-21.

72. Tannock IF et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med. 2004;351(15):1502-12.

73. Tombal B, Berges R. Optimal control of testosterone: a clinical case-based approach of modern androgen-deprivation therapy. Eur Urol Suppl. 2008;7(1):15-21.

74. Morote J et al. Redefining clinically significant castration levels in patients with prostate cancer receiving continuous androgen deprivation therapy. J Urol. 2007;178(4 Pt 1):1290-5.

75. Lawrentschuk N et al. Efficacy of a second line luteinizing hormone-releasing hormone agonist after advanced prostate cancer biochemical recurrence. J Urol. 2011;185(3):848-54.

76. Tombal B. Non-metastatic CRPC and asymptomatic metastatic CRPC: which treatment for which patient? Ann Oncol. 2012;23 Suppl 10:x251-8.

77. Baskin-Bey ES et al. TERRAIN: A randomized, double-blind, phase II study comparing MDV3100 with bicalutamide (Bic) in men with metastatic castrate-resistant prostate cancer (CRPC). Abstract TPS4698^. ASCO Annual Meeting, Chicago, IL, USA, 1–5 June 2012.

78. Gillessen S et al. Management of patients with advanced prostate cancer: recommendations of the St Gallen Advanced Prostate Cancer Consensus Conference (APCCC) 2015. Ann Oncol. 2015;26(8):1589-604.

79. Li Z et al. Conversion of abiraterone to D4A drives anti-tumour activity in prostate cancer. Nature. 2015;523(7560):347-51.

80. de Bono JS et al. Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med. 2011;364(21): 1995-2005.

81. Ryan CJ et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. N Engl J Med. 2013;368(2):138-48.

82. Tran C et al. Development of a second-generation antiandrogen for treatment of advanced prostate cancer. Science. 2009;324(5928):787-90.

83. Hu R et al. Molecular processes leading to aberrant androgen receptor signaling and castration resistance in prostate cancer. Expert Rev Endocrinol Metab. 2010;5(5):753-64.

84. European Medicines Agency (EMA). Meeting highlights from the Committee for Medicinal Products for Human Use (CHMP) 20–23 October 2014. 2014. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2014/10/news_detail_002191.jsp&mid=WC0b01ac058004d5c1. Last Accessed: 17 January 2014.

85. Loriot Y et al. Effect of enzalutamide on health-related quality of life, pain, and skeletal-related events in asymptomatic and minimally symptomatic, chemotherapy-naive patients with metastatic castration-resistant prostate cancer (PREVAIL): results from a randomised, phase 3 trial. Lancet Oncol. 2015;16(5):509-21.

86. Gravis G et al. Androgen-deprivation therapy alone or with docetaxel in non-castrate metastatic prostate cancer (GETUG-AFU 15): a randomised, open-label, phase 3 trial. Lancet Oncol. 2013;14(2):149-58.

87. Sweeney CJ et al. Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer. N Engl J Med. 2015;373(8):737-46.

88. Gravis G et al. Androgen deprivation therapy plus docetaxel versus ADT alone for hormone-naive metastatic prostate cancer: Long-term analysis of the GETUG-AFU 15 phase III trial. Abstract 140. Genitourinary Cancers Symposium. Orlando, Florida, 26–28 February 2015.

89. Gravis G et al. Androgen Deprivation Therapy (ADT) Plus Docetaxel Versus ADT Alone in Metastatic Non castrate Prostate Cancer: Impact of Metastatic Burden and Long-term Survival Analysis of the Randomized Phase 3 GETUG-AFU15 Trial. Eur Urol. 2015. [Epub ahead of print].

90. Medical Research Council. STAMPEDE: Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy: A Multi-Stage Multi-Arm Randomised Controlled Trial. NCT00268476. http://www.clinicaltrials.gov/ct2/show/NCT00268476.

91. James ND et al. Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. Lancet. 2015. [Epub ahead of print].

92. Vale CL et al. Addition of docetaxel or bisphosphonates to standard of care in men with localised or metastatic, hormone-sensitive prostate cancer: a systematic review and meta-analyses of aggregate data. Lancet Oncol. 2015. [Epub ahead of print].

93. Taplin ME et al. Intense androgen-deprivation therapy with abiraterone acetate plus leuprolide acetate in patients with localized high-risk prostate cancer: results of a randomized phase II neoadjuvant study. J Clin Oncol. 2014;32(33):3705-15.

94. Dana-Farber Cancer Institute; Medivation, Inc. Enzalutamide/Leuprolide +/- Abiraterone/Pred in Prostate. NCT02268175. https://clinicaltrials.gov/ct2/show/NCT02268175.

95. Medivation, Inc. Safety and Efficacy Study of Enzalutamide Plus Leuprolide in Patients With Nonmetastatic Prostate Cancer (EMBARK). NCT02319837. https://clinicaltrials.gov/ct2/show/NCT02319837.

96. Aragon Pharmaceuticals, Inc. A Study of JNJ-56021927 (ARN-509) and Abiraterone Acetate in Participants With Metastatic Castration-Resistant Prostate Cancer. NCT02123758. https://clinicaltrials.gov/ct2/show/NCT02123758.

97. Herr HW. A comparison of the quality of life of patients with metastatic prostate cancer who received or did not receive hormonal therapy. Cancer. 1993;71(3 Suppl):1143-50.

98. Alibhai SM et al. Long-term side effects of androgen deprivation therapy in men with non-metastatic prostate cancer: a systematic literature review. Crit Rev Oncol Hematol. 2006;60(3):201-15.

99. Saylor PJ, Smith MR. Metabolic complications of androgen deprivation therapy for prostate cancer. J Urol. 2009;181(5):1998-2006.

100. Keating NL et al. Diabetes and cardiovascular disease during androgen deprivation therapy: observational study of veterans with prostate cancer. J Natl Cancer Inst. 2010;102(1):39-46.

101. O'Farrell S et al. Risk and Timing of Cardiovascular Disease After Androgen-Deprivation Therapy in Men With Prostate Cancer. J Clin Oncol. 2015;33(11):1243-51.

102. Basaria S et al. Long-term effects of androgen deprivation therapy in prostate cancer patients. Clin Endocrinol (Oxf). 2002;56(6):779-86.

103. Diamond T et al. The effect of combined androgen blockade on bone turnover and bone mineral densities in men treated for prostate carcinoma: longitudinal evaluation and response to intermittent cyclic etidronate therapy. Cancer. 1998;83(8):1561-6.

104. Chen AC, Petrylak DP. Complications of androgen-deprivation therapy in men with prostate cancer. Curr Urol Rep. 2005;6(3):210-6.

105. Newton C et al. Memory complaints associated with the use of gonadotropin-releasing hormone agonists: a preliminary study. Fertil Steril. 1996;65(6):1253-5.

106. Harrington JM et al. Body image perceptions in men with prostate cancer. Oncol Nurs Forum. 2009;36(2):167-72.

107. Harrington JM, Badger TA. Body image and quality of life in men with prostate cancer. Cancer Nurs. 2009;32(2):E1-7.

108. Matthew AG et al. Sexual dysfunction after radical prostatectomy: prevalence, treatments, restricted use of treatments and distress. J Urol. 2005;174(6):2105-10.

109. Wassersug RJ. Mastering emasculation. J Clin Oncol. 2009;27(4):634-6.

110. Nguyen PL et al. Adverse effects of androgen deprivation therapy and strategies to mitigate them. Eur Urol. 2015;67(5):825-36.

111. Bayoumi AM et al. Cost-effectiveness of androgen suppression therapies in advanced prostate cancer. J Natl Cancer Inst. 2000;92(21):1731-9.