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REVIEW

How to Improve the Quality of Life of Patients with Prostate Cancer Treated with Hormone Therapy?

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Abstract: Prostate cancer (PC) is a hormone-sensitive tumor. Androgen deprivation therapy (ADT) is the cornerstone of systemic therapy for patients with intermediate or high-risk localized, recurrent, and metastatic prostate cancer. Although generally well tolerated, ADT can lead to short- and long-term adverse events that can worsen the quality of life of patients with PC. In the last decade, the introduction of novel generation androgen receptor pathway inhibitors (ARPI) has resulted in an improvement in the prognosis of patients with metastatic PC when used in combination with ADT. The use of ARPI in increasingly early stages of the disease determines a longer exposure of patients to these treatments. Although ARPIs are normally well-tolerated drugs, they generally cause an increase in toxicity compared to ADT alone, being able to worsen some adverse events already induced by ADT or leading to the development of specific side effects. Although there are no specific treatments for all the adverse events induced by hormonal therapies, it is essential to know the possible toxicities induced by the different treatments and to start procedures to prevent and/or recognize and consequently treat them early in order to not compromise the quality of life of the patients with PC. The aim of this review is to describe the adverse events induced by hormonal therapies. We will first describe the side effects induced by both ADT and ARPI and then the specific adverse events of the different ARPIs. Furthermore, we will try to highlight the possible therapeutic options to prevent or mitigate the toxicity induced by hormone therapies in order to improve the quality of life of the patients with PC.

Keywords: prostate cancer, androgen deprivation therapy, androgen pathway inhibitors, management of adverse events

Introduction

Prostate cancer (PC) is the second most frequent cancer and the leading cause of cancer death among men.[1,2] Due to the significant androgens dependence, since 1940 androgen deprivation therapy (ADT) has represented the cornerstone of systemic treatment for men with PC.[3] According to the current international guidelines, ADT is used in patients with intermediate or high-risk localized, recurrent and metastatic PC.[4,5] About 50% of patients with PC will receive ADT at some point during their treatment.[6] ADT consists of bilateral orchiectomy or luteinizing hormone–releasing hormone (LHRH) agonists and antagonists.[6,7] LHRH agonists and antagonists act by suppressing the hypothalamic–pituitary–gonadal axis, and consequently lowering the circulating testosterone levels.[6,7] After chemical or surgery castration, the incorporation of androgens into the cell nucleus continues, as a result of their production by the adrenal glands. This can be counteracted by adding an antiandrogen to ADT.[7,8] First-generation antiandrogens (eg bicalutamide) compete with circulating androgens for binding sites on the androgen receptor (AR) within the prostate cells.[8] To date, bicalutamide is used for about a month to prevent the flare-up phenomenon in patients starting LH-RH agonist or as an alternative to ADT in combination with salvage radiotherapy in case of biochemical recurrence after radical prostatectomy.[7,8]

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A better understanding of AR functioning and ADT resistance mechanisms has led to the development of novel generation androgen receptor pathway inhibitors (ARPI) such as abiraterone, enzalutamide, apalutamide and darolutamide.[9–13] Initially used only in patients with metastatic PC who became resistant to ADT (metastatic castration-resistant prostate cancer, mCRPC),[14–17] ARPI have subsequently been shown to be effective when used in combination with ADT in earlier settings of the disease such as patients with non-metastatic castration resistant (nmCRPC),[13,18,19] metastatic hormone-sensitive (mHSPC) disease,[10–12,20–25] and recently also in those with high-risk localized disease according to the STAMPEDE criteria.[22] The anticipation of ARPIs in earlier stages of the disease resulted in longer exposure and deeper androgen suppression in patients with PC and consequently a higher risk of developing adverse events. For example, in the ARCHES trial, there was an increase in the frequency of adverse events in patients treated with ADT + enzalutamide according to the treatment duration: fatigue, hypertension, cognitive/memory impairment and falls occurred, respectively, in 24.1%, 8.6%, 4.5% and 3.7% of patients after a median treatment duration of 12.8 months[21] while after a median treatment duration of 40.2 months they were 32.2%, 14.3%, 6.6% and 10.1%, respectively.[23]

Although both ADT and ARPI are generally well tolerated, they can still cause both short and long-term adverse events that can compromise quality of life and consequently treatment compliance of patients with PC.[24–26] This review aims to describe the adverse events associated with ADT, first-generation antiandrogens and ARPI and to provide evidence-based strategies to mitigate or prevent them in order to try to improve the quality of life of patients with PC.

Cardiovascular Complications

In patients with PC cardiovascular diseases were the most common causes of non PC-related deaths.[24,27] The role of ADT as a possible cardiovascular risk factor remains controversial.[28–30]

LHRH agonists are associated with increased low-density lipoprotein cholesterol and triglyceride levels, increased visceral fat, decreased lean body mass, increased insulin resistance, and decreased glucose tolerance.[24,26,31] These changes can accelerate atherosclerosis and predispose the patient to coronary artery disease. ADT has also been associated with both arterial thromboembolic events and venous thromboembolic events, ultimately increasing the rate of acute myocardial infarction, heart failure, and arrhythmias, with overall increased cardiovascular morbidity and mortality.[32–35] In a meta-analysis by Zhao et al including over 119.000 PC patients, ADT was associated with a significant risk of cardiovascular mortality [hazard ratio (HR) 1.17, 95% confidence interval (CI) 1.04–1.32, p= 0.01].[28] In another meta-analysis, Bosco et al found a 38% increase in cardiovascular disease for patients with PC treated with ADT compared to those without [relative risk (RR) 1.38, 95% CI 1.29–1.48].[31] In contrast, in a meta-analysis performed by Nguyen that included over 4.000 patients with PC the use of ADT lowers PC specific and all-cause mortality without increasing risk of cardiovascular death (RR, 0.93; 95% CI, 0.79–1.10; P = 0.41).[30]

The presence of pre-existing heart disease appears to be a risk factor for development of major adverse cardiac events (MACE) in patients with PC receiving ADT.[33–35] O'Farrell et al showed that patients who experienced two or more MACE before initiation of ADT were at highest risk for developing cardiovascular disease during the first six months of therapy compared to an age-matched cohort from the general population.[33] Ziehr et al found no association between ADT and cardiac-specific mortality in patients without cardiovascular comorbidity, while patients with a history of congestive heart failure or a previous myocardial infarction treated with ADT had a significantly higher risk of cardiac mortality compared to those without treatment (HR 3.28, 95% CI 1.01–10.64, p=0.048).[34] Importantly, even short durations of ADT (3–6 months) appear to increase cardiovascular risk.[35]

An important area of debate is whether there is a different risk profile for cardiovascular events between LHRH agonists and antagonists. Studies in animal models suggest that LHRH agonists, but not antagonists, may induce atherosclerotic plaque instability and rupture[36,37]. The rupture of the atherosclerotic plaque is caused by a degradation of the cap connective tissue by infiltrating macrophages. Lymphocytes T-helper 1 (Th1) type are important macrophage activators and are the dominant T-cell type in atherosclerotic plaques. T cells express LHRH receptors, and activation of these receptors has been shown to stimulate T-cell expansion and differentiation into the Th1 phenotype, suggesting that LHRH agonists may promote destabilization of atherosclerotic plaques.[38] In the last 3 years, the results of 3 randomized clinical trials have been published that evaluated the cardiovascular toxicity profile of LHRH agonists compared to antagonists.[39–41] An open-label

Phase 2 study randomized 80 patients with pre-existing MACE, to receive LHRH agonists or antagonists for 1 year and included new cardiovascular events as a secondary end point. In this trial, Margel et al found that patients using a LHRH antagonist were 18% less likely to experience a major cardiovascular or cerebrovascular at 12 months (p=0.032).[39] The Phase III HERO trial compared the oral LHRH antagonist relugolix versus leuprolide among 622 patients with advanced PC.[40] More than 90% of patients had cardiovascular risk factors and 15% had a history of MACE. In a prespecified safety analysis, patients treated with relugolix had a 2.9% incidence of MACE within the first 12 months of treatment compared to 6.2% in the leuprolide arm, which represented a 54% decrease in risk of developing MACE (HR 0.46, 95% CI 0.24–0.88).[40] In patients with a prior medical history of MACE, the incidence of new MACE appeared to be more pronounced in the leuprolide arm (17.8% vs 3.6%).[40] The PRONOUNCE trial is the first, international, randomized, Phase 3 trial to prospectively compare the cardiovascular safety of an LHRH antagonist (degarelix) and an LHRH agonist (leuprolide) in patients with PC and preexisting atherosclerotic cardiovascular disease.[41] The trial was terminated early because of incomplete accrual and a low event rate. Regardless, subsequent MACE did not differ between antagonist and agonist at 1 year (5.5% v 4.1%, respectively; P= 0.53).[41]

The increased cardiovascular risk in patients treated with ADT may also be due to the body modifications and metabolic alterations it causes.[42–45] ADT in fact determines an increase in body weight and percentage fat mass and a loss of muscle mass configuring the sarcopenic obesity profile. Patients with this metabolic profile have a decrease in absolute muscle strength, aerobic fitness, and general physical function, which overall may contribute to morbidity by increasing falls and fracture risk, which finally may negatively impact on overall survival.[42–45] These changes are thought to occur soon after initiating therapy, sometimes as early as one month following treatment and these changes may persist up to two years beyond treatment cessation.[45] The metabolic consequences of ADT include insulin resistance and changes to lipid profile with an increase in triglyceride and total cholesterol levels, predisposing to the developing a metabolic syndrome.[26] A meta-analysis demonstrated a 75% higher risk of metabolic syndrome and a 36% higher risk of diabetes in patients on ADT compared to controls.[42–46] Metformin and statins have been investigated as a potential treatment for ADT-induced metabolic changes with promising results. In a prospective, randomized study of 40 patients with PC, six months of metformin combined with exercise resulted in decreased abdominal girth, BMI, and blood pressure.[46] Furthermore, in a systematic review and meta-analysis, He et al showed that ADT with metformin improves overall survival (OS) (HR = 0.72, 95% CI: 0.59–0.88, P = 0.001).[47] In a systematic review of nearly 120,000 PC patients statin use was associated with a 27% reduction in the risk of overall mortality (HR 0.73, 95% CI 0.66–0.82).[48] However, randomized controlled trials are warranted to validate these findings.

ADT is also associated with a prolongation of the QT interval and, therefore, theoretically increased risk of arrhythmia sudden cardiac death.[49]

Treatment with ARPI can also lead to an increased cardiovascular risk. In the meta-analysis by Iacovelli et al, including 6 phase 2 and 3 trials testing enzalutamide and abiraterone in mCRPC patients, the addition of ARPI to the ADT resulted in an increase in cardiovascular events of 36% compared with ADT alone (RR 1.36, 95% CI, 1.13–1.64; p=0.001), even if the absolute difference in terms of all- and grade 3–4 events incidence was small (14% and 4%, respectively).[50] In particular, the addition of abiraterone resulted in a significant increase in cardiovascular toxicity, whereas enzalutamide does not.[50] These results were confirmed by the meta-analysis by Moreira et al.[51] The increased cardiovascular risk induced by abiraterone is determined by its mechanism of action. As a result of CYP17 inhibition, as well as a reduction in testosterone levels, abiraterone induces a decrease in glucocorticoid production and a compensatory increase in adrenocorticotrophic hormone (ACTH), resulting in a rise in steroids with mineralocorticoid properties upstream of CYP17A1, which may result in a syndrome of secondary mineralocorticoid excess, characterized by water retention, hypertension and the possible development of heart failure.[50] On the other hand, enzalutamide has been associated with statistically significant QTc prolongation (mean increase of 3–6.5 ms from baseline during weeks 5–25).[52]

In a patient with PC, before starting treatment with ADT, it is important to take a careful medical history to investigate the presence of risk factors or cardiovascular diseases. Basal assessment should consist of blood tests including lipid and glycemic profile, ECG, blood pressure assessment and BMI calculation. In patients with a high cardiovascular risk or with cardiac comorbidities that are not well controlled it may be useful to perform a cardiological evaluation to try to optimize the patient's cardiovascular profile before starting ADT. In these patients, it may be useful to

use LHRH antagonists, although there is no clear evidence for this recommendation. In patients without cardiovascular risk factors, the same recommendations as for the general population are suggested. In particular, it is recommended to perform regular physical activity, to follow a varied and balanced diet, not to smoke and to limit the use of alcohol.[24] When it is indicated to add an ARPI to the ADT it is suggested to also perform an echocardiogram. In case of cardiovascular comorbidities or impaired cardiac function, it is recommended to avoid treatment with abiraterone and to prefer another ARPI. In patients with a known history of QT prolongation or patients who are taking medications known to prolong the QT interval monitoring of ECG and serum electrolyte levels at baseline and during treatment with enzalutamide should be considered.[52]

Bone Health

Hormones play a crucial role in bone homeostasis.[53,54] AR is present in chondrocytes and osteoblasts and the activated AR interacts with osteoblast precursors stimulate bone formation through upregulation of transforming growth factor (TGF) -β, insulin-like growth factors-1 (IGF-1) and fibroblast growth factor (FGF) and downregulate Interleukin 6 (IL-6), which stimulates osteoclastogenesis.[53,54] Furthermore, dihydrotestosterone has been shown to reduce osteoprotegerin (OPG) levels, which stimulates osteoclast activity.[53,54] Therefore, the use of hormone therapies that can reduce androgen levels, such as ADT inevitably, have a negative effect on bone health. From a molecular point of view testosterone deficiency promotes the activation of nuclear factor kappa B ligand (RANKL) production from osteoblasts, which contributes to the promotion of the differentiations and functions in osteoclasts leading to an increase in bone resorption and a reduction in bone mineral density (BMD).[55] In addition, low testosterone levels lead to a reduction in the expression of IGF-1 and IGF-binding protein (IGF-BP) in osteoblasts, two molecules essential for differentiation and proliferation of chondrocytes and osteoblasts.[53,54] Furthermore, the downregulation of OPG enhances osteoclast recruitment and activation leading to further worsening of bone loss.[53,54]

ADT-related loss of BMD is estimated to be around 4–6% per year with a more rapid loss during the first year of treatment (5–10%), which significantly exceeds that of normal age-related (0.5–1.0% per year) and postmenopausal women (1–2.3% per year), and is about two-fold that of women with breast cancer treated with aromatase inhibitors.[56,57] Through the reduction of BMD, ADT increases the risk for patients with PC of developing osteoporosis and consequently of skeletal fractures. Taylor et al showed in more than 100.000 patients with PC that ADT increased risk of for skeletal fracture (RR 1.23, 95% CI, 1.10–1.38).[58] In another large retrospective cohort study, men treated with ADT experienced more fragility fractures than matched controls (10.8% vs 3.2%; $p < 0.0001$). The use of ADT was also associated with a 1.82-fold increase in risk of hip fracture requiring hospitalisation.[59] In addition, fractures are known to be associated with increased mortality risk, and thus may be an important prognostic factor for patients with PC. In fact, patients with PC experiencing a fracture had a 1.38-fold higher overall mortality risk than those who did not (95% CI, 1.34–1.43).[55] Additionally, in patients with PC, bone health is frequently already suboptimal before starting ADT due to age and comorbidities. Cheung et al showed that before starting ADT, 11% of patients with PC had osteoporosis and 40% osteopenia.[60] These results reflect the need for a thorough screening of bone loss prior to initiation of ADT. The gold standard for measuring BMD is Dual-energy X-ray absorptiometry (DEXA).[61] However, in patients treated with ADT the risk of fracture is often independent of DEXA values and it is frequently misclassified when based only on DEXA measurement.[62] This occurs because ADT determines not only a reduction in BMD (generally slow and reversible) but also a qualitative damage to the trabecular microstructure (often rapid and not reversible).[62,63] In fact, the high bone turnover induced by ADT determines a thinning and then the perforation of bone trabeculae which increases the risk of skeletal fractures which, however, can not be measured by DEXA.[63] In fact, in the study by Greenspan et al many of the patients with PC undergoing ADT who experienced a vertebral fracture had fewer trabecular plaques and a higher erosion index than men without fracture despite having a normal BMD value on DEXA.[62]

In patients with PC treated with ADT, fractures typically occur during the first year and this observation reinforces the fact that skeletal fragility is prominently dependent on rapid microarchitectural damage of the bone trabeculae rather than on the low bone mass.[63] To improve fracture risk assessment, the World Health Organization has computed a FRAX algorithm that accounts for demographic risk factors, alcohol/tobacco/glucocorticoid use and other relevant past personal or familial history.[63] The FRAX tool calculates the probability of risk for bone fracture for the next 10 years.[63] However,

this tool does not include ADT treatment among the risk factors for developing skeletal fractures, therefore the FRAX score may also underestimate the risk in patients with PC treated with ADT.[63] According to the ESMO guidelines, the management of bone health in patients treated with ADT is based on the criteria of Coleman et al.[64] All patients starting ADT should be recommended and adequate calcium intake (1200 mg daily total from diet and supplements) and vitamin D supplementation (800–2000 IU daily). Additionally, patients should be encouraged to make lifestyle changes such as trying to quit smoking, reducing alcohol consumption and increasing physical activity. In patients who have a T score <2 or the presence of at least 2 risk factors for fracture (age >65; T score <-1.5; smoking; BMI <24; family history of hip fracture; personal history of fragility fracture above age 50; oral glucocorticoid use for >6 months) the use of bone-protecting agents (BPA) should be considered.[64] In patients who do not meet these criteria, the risk of fractures should be monitored by repeating a DEXA every 1–2 years.[64] Since Coleman's criteria are mainly based on the BMD value and considering that, as previously mentioned, BMD does not exactly reflect the fracture risk, the exclusive use of these criteria to establish the use of BPA can lead to under-treatment in patients with PC treated with ADT. Therefore, BPA should probably be used as primary prevention in all patients who initiate ADT regardless of Coleman's criteria.[65] BPA should be started as soon as possible in patients undergoing ADT considering that most fractures occur within one year of starting ADT. Finally, BPA should be performed for the entire duration of the ADT as the risk of fracture has been shown to increase with increasing duration of ADT. A new DEXA should be performed at the end of ADT to evaluate whether to continue treatment with BPA.[65]

The most commonly used BPAs to reduce the fracture risk of PC patients treated with ADT are bisphosphonates (eg 70mg alendronic acid per week) and denosumab (60mg every 6 months).[55] Bisphosphonates are analogues of pyrophosphate, a normal component of the bone matrix and act by inhibiting the enzyme farnesyl diphosphonate synthase resulting in a reduced ability of the osteoclast to bind to bone, thus compromising their bone resorption activity.[61] Instead, denosumab is a human monoclonal RANKL antibody that acts by inhibiting the RANK – RANKL pathway, thus hindering osteoclast activity.[61] Bisphosphonates have been shown to be effective in preventing ADT-induced bone, or increasing lumbar spine and hip BMD, although they have not been shown to reduce the risk of fractures.[55] Denosumab is the only BPA that showed to reduce the risk of fractures in patients with PC treated with ADT.[55] In the multicenter, double-blind HALT trial denosumab every six months showed to reduce the incidence of new vertebral fractures at 3 years by 62% compared with placebo (relative risk 0.38, 95% CI 0.19–0.78, p = 0.006) in patients with non-metastatic PC undergoing ADT.[66] Finally, in patients with metastatic castration-resistant PC (mCRPC), bisphosphonates (eg zoledronate 4mg every 4 weeks) and denosumab (120mg every 4 weeks) are used to reduce skeletal-related events, such as pathological fracture, radiotherapy to bone, surgery to bone, spinal cord compression and hypercalcaemia.[67,68]

While the relationship between ADT and bone health is known, there is little evidence on the effect of antiandrogens and ARPIs. In a prospective observational study, LHRH agonist plus bicalutamide did not result in a significant increase in osteopenia or osteoporosis compared to LHRH agonist alone in 312 patients with PC (p= 0.3688).[69] On the contrary, Wang et al observed a 2.11-fold increase in fracture risk among patients treated with antiandrogens alone and the combination of LHRH agonist and antiandrogen had the greatest risk of fracture compared to antiandrogen and LHRH agonist monotherapy (OR = 3.48; 95% CI 3.07–3.96).[59] There is also little evidence on the effect of intermittent ADT on bone health, although some results seem to suggest that it may lead to a reduction in fracture risk compared to continuous ADT.[70] Results from PROSPER and SPARTAN trials suggest that treatment with ARPI further increases the fracture risk in patients with non-metastatic castration-resistant PC treated with long term ADT.[18,19] Finally, in the PEACE-1 study, the addition of abiraterone to ADT + docetaxel in patients with metastatic hormone-sensitive PC was associated with a modest increase in bone loss over the first 2 years.[71] Therefore, it is unclear if a more potent inhibition of testosterone activity may increase bone turnover leading to an increased risk of fractures.

Cognitive Disorders

Several studies have shown that ADT can produce a negative effect on cognitive functioning in about 25–50% of patients.[72,73] Patients receiving ADT could experience difficulties with verbal memory, spatial abilities and attention.[24,74] Impairment can already be evident 6–12 months after the beginning of treatment.[75] Furthermore, ADT may be associated with development of depressive symptoms. Specifically, ADT has been associated with increased rates of major

depression and worsening depressive symptoms without an increased risk of suicidality.[76] An association has also been shown between low level of testosterone and the risk of dementia and/or Alzheimer disease.[77] In the systematic review and meta-analysis conducted by Motlagh et al, the risk of new onset dementia and Alzheimer disease was higher in patients with PC who received ADT compared to those who did not (HR 1.21, 95% CI 1.11–1.33 and HR 1.16, 95% CI 1.09–1.24).[77] Androgen receptor messenger RNA was found to be expressed in cortical brain regions that are critical for cognitive functions (eg the prefrontal cortex, parietal lobe and hippocampus). Studies used functional magnetic resonance imaging to assess the effect of ADT on cerebral structures showed a decrease in the gray matter volume in the frontopolar cortex, dorsolateral prefrontal cortex and primary motor cortex in patients with PC under ADT.[78] Furthermore, a low testosterone level increases the production of extracellular beta amyloid protein and intracellular tau phosphorylation. Accumulation of these proteins in the central nervous system is a pathological feature of Alzheimer disease.[79]

The effect of ARPIs on the cognitive functions of PC patients has not been adequately evaluated in the pivotal studies.[80] Apalutamide and enzalutamide, have been associated with adverse central nervous system-related events in patients with PC, including fatigue and mental impairment disorders.[81] In contrast, limited data suggest fewer drug-related cognitive effects with abiraterone compared with enzalutamide.[82,83] In clinical trials, darolutamide was not associated with a higher incidence of adverse cognitive effects.[13] The alteration of cognitive functions reported with apalutamide and enzalutamide may be due to their penetration of the blood–brain barrier, whereas darolutamide has shown limited blood–brain barrier penetration in preclinical and clinical studies.[81]

Cognitive dysfunction may be more prevalent in real-world populations than in the carefully selected populations included in phase III studies. For example, in the observational AQUARiUS study, clinically meaningful worsening in perceived cognitive impairment was reported by 49% of patients treated with abiraterone and 76% of those who received enzalutamide ($p = 0.05$).[82] By contrast, in REAAcT trial, patients treated with abiraterone or enzalutamide had almost no change from baseline in cognitive function over time.[83]

Based on these findings, all patients starting ADT should be counseled regarding possible neuropsychiatric side effects, including information about the connection between ADT and mental health[24] (Table 1). Screening for cognitive dysfunction should be considered an integral part of standard management before initiation of hormone therapies. Furthermore, in patients with PC and diagnosed with depression or dementia it would be useful to perform a psychiatric or geriatric evaluation before starting hormone therapy. In addition, routine monitoring of cognitive function should be performed in patients receiving hormone therapies to detect any cognitive deficits as soon as possible and, if necessary, specialized neuropsychological evaluation should be performed. There are several simple questionnaires that can help the physician in recognizing the presence of cognitive alterations at an early stage, such as the Mini-Mental State Examination (MMSE), the Montreal Cognitive Assessment (MoCA) or Mini-Cog assessment.[81] However, to date none of these tools are routinely used in clinical practice in monitoring PC patients treated with hormone therapies. A therapeutic strategy to improve the quality of life of patients with PC by reducing the risk of developing cognitive disorders could be represented by the use of intermittent hormonal therapy. In a trial with more than 1500 patients with mHSPC Hussain et al showed that intermittent ADT was associated with better mental health at month 3 ($p=0.003$) even if this improvement was not present at a longer follow-up.[70]

Hot Flashes

Hot flashes are defined as an intense heat sensation, flushing and diaphoresis that usually involve the face and trunk, sometimes associated with anxiety and palpitations.[24] They are one of the most frequent adverse events of ADT occurring in up to 80% of patients and it is reported as the most bothering from 27% of them.[84]

Hot flashes can be associated with sleep disturbance and may lead to a deterioration in quality of life.[85] Moreover they may decrease compliance to ADT and are a major contributor to its discontinuation.[24]

Literature suggests that estrogen and androgen withdrawal disrupt the equilibrium of the neurotransmitters, norepinephrine and serotonin. This consequently affects the omeostatic mechanism in the thermoregulatory zone in the pre-optic zone of the hypothalamus.[86] Antiandrogens have a significantly lower risk of hot flashes than LHRH agonists (<1% vs 45%) and intermittent ADT is associated with significantly better scores for hot flashes compared to continuous ADT ($p<0.001$).[24,87]

Table 1 Summary of Adverse Events Associated with Hormone Therapies and Their Management

Complication	Summery of Events	Physiopathology	Management
Cardiovascular disease[47,48]	• Increased risk of cardiac events • Increased risk of stroke • Insulin resistance/glucose intolerance • Altered lipid profiles • Increased risk for metabolic syndrome • Increased risk of heart failure with abiraterone treatment	• Endothelial dysfunction • Proinflammatory factors • Procoagulant state • Increase in aldosterone levels and therefore in mineralocorticoid activity induced by abiraterone	1. Lifestyle changes to promote healthy diet 2. Smoking cessation 3. Exercise therapy 4. Monitoring and medical optimization of cardiovascular risk factors (eg hypertension, diabetes, dyslipidemia) 5. Prefer an LHRH agonist in patients with cardiovascular comorbidities 6. Perform a cardiological evaluation in patients at high risk of developing cardiovascular events 7. Perform basal assessment of lipid and glycemic profile, ECG, blood pressure assessment and BMI calculation before starting ADT 8. Perform echocardiogram before starting ARPI 9. Carefully monitor patients with pre-existing cardiovascular comorbidity treated with abiraterone
Bone health[55–57]	• Decreased BMD • Increased risk for osteoporosis • Increased risk for clinical fractures	• Increases bone turnover • Qualitative alterations of the bone microarchitecture	1. Smoking and alcohol cessation 2. Adequate calcium intake (1200 mg daily) and vitamin D 3. Supplementation (800–1000 IU daily) 4. Perform bone densitometry 5. Exercise therapy: resistance + aerobic training 6. Consider BPA (eg 70mg alendronic acid per week) or denosumab (60mg every 6 months) for all patients regardless BMD value 7. Use zoledronate (4mg every 4 weeks) or denosumab (120mg every 4 weeks) in all patients with mCRPC and bone metastases
Cognitive disorders[76,77]	• Alteration of concentration • Memory impairment • Dementia • Depression	• Decrease in the gray matter volume in the frontopolar cortex, dorsolateral prefrontal cortex and primary motor cortex • Increased production of extracellular amyloid-beta protein and intracellular phosphorylation of tau	1. Consider screening for cognitive dysfunction before starting ADT using specific tools 2. Perform a psychiatric or geriatric evaluation in patients diagnosed with depression or dementia. 3. Routine monitoring of cognitive function during hormonal treatment
Hot flashes[90]		• Disruption of the omeostatic mechanism in the thermoregulatory zone in the pre-optic zone of the hypothalamus by alteration of equilibrium	1. Avoid heat or spicy food 2. Alteration of the homeostatic mechanism in the thermoregulatory zone in the preoptic zone of the hypothalamus 3. Evaluate hormonal (megestrol or cyproterone acetate) or non hormonal drugs (gabapentin, venlafaxine) or acupuncture.

(*Continued*)

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Table 1 (Continued).

Complication	Summery of Events	Physiopathology	Management
Breast events[97]	• Gynecomastia • Mastodynia		1. Prophylactic treatment with tamoxifen or low-dose radiotherapy 2. Surgical management for select patients
Fatigue and anemia[102]		• Decrease of testosterone- induced erythropoiesis • Decrease of testosterone induced renal production of erythropoietin	1. Physical exercise and dietary counselling 2. Investigate and treat secondary causes of anemia 3. Monitor Hb levels during hormonal treatments
Sexual disfunction[98]	• Decreased penile and testicular size • Loss of libido • Decreased sensitivity to sexual stimulation • Erectile dysfunction		1. Appropriate pre-treatment counselling 2. Consider psychosocial support 3. Consider phosphodiesterase inhibitors 4. Consider intermittent ADT
Renal toxicity[103]	• Acute kidney injury	• ADT may antagonize the vasodilating effects of testosterone on renal vessels • estrogen deficiency can negatively affect renal tubular function	1. Monitor creatinine levels and glomerular filtration rate before and during treatment with ADT

First in patients who report frequent hot flashes lifestyle modifications may be recommended, including avoidance of potential patient-identified triggers, commonly heat or spicy food[88] (Table 1). In addition, several pharmacological hormonal and non-hormonal agents have been assessed in the treatment of hot flashes, however few evidences exist for their management.

In several small prospective studies, the use of diethylstilbestrol resulted in complete resolution of hot flashes in more than 70% of patients.[86] A double-blind, randomized study showed a 75–80% reduction of hot flashes in patients treated with megestrol acetate versus placebo, but it is associated with an increase PC growth.[89] Cyproterone acetate showed similar results without the risk of tumour progression.[90]

Gabapentin, used as an anticonvulsant and for treatment of neuropathic pain, was evaluated for the treatment of hot-flashes. In a randomized trial, 214 patients with PC treated with ADT were randomized to placebo, or gabapentin at the dosage of 300, 600 or 900 mg.[91] There were reductions in hot flash scores by 22%, 23%, 32%, and 46%, respectively, without increased toxicity with gabapentin compared with placebo.[91] Based on these data, gabapentin is a reasonable therapy to treat ADT-induced hot flashes with a starting dose at 300 mg daily augmentable up to 900 mg.

Venlafaxine, a serotonin-norepinephrine reuptake inhibitor used as antidepressant drug, was also tested in patients with PC with the aim of reducing hot flashes. In a randomized clinical trial in PC patients treated with ADT venlafaxine was compared to medroxyprogesterone acetate and cyproterone acetate and showed to reduce hot flashes of 47.2% although cyproterone and medroxyprogesterone obtained better results (−94.5% and −83.7% respectively).[90]

To mitigate the hot flashes in patients with PC treated with ADT, it has also been investigated the role of complementary medicine, such as the acupuncture. It leads to a decrease of hot flash symptoms by 89–95%, however, these results are not based on randomized clinical trials data.[92] Finally, the use of intermittent ADT showed a reduction in hot flashes compared to continuous ADT ($p<0.01$).[93]

In the pivotal trials, the addition of ARPI to ADT appears to result in an increased incidence of hot flashes compared to ADT alone. In the AFFIRM[16] and PREVAIL[17] studies, 18–20% of patients treated with ADT + enzalutamide experienced hot flushes versus 8–10% of patients treated with ADT alone. In COU-AA-302 trial,[15] patients experiencing hot flushes were 22% in the ADT + abiraterone group and 18% in the ADT alone group, respectively. Similar findings in the TITAN[11] study where adding apalutamide to ADT resulted in an approximately 6% increase in hot flashes. On the other hand, darolutamide does not seem to increase the incidence of hot flushes: in the ARAMIS study,[13] 5.2% of patients in the darolutamide arm developed hot flushes versus 4.2% in the placebo group.

Breast Events

Breast events include gynecomastia and mastodynia, which may occur concurrently or separately. Gynecomastia occurs most commonly with antiandrogens while is a rare complication of ADT.[94]

ARPI does not appear to increase breast events compared to antiandrogen: in the Phase 3 study ENZAMET, the frequency of breast events was similar in patients treated with ADT + enzalutamide compared to ADT + antiandrogen.[12] Several studies have demonstrated that both tamoxifen and radiotherapy are effective prophylactic treatments for breast events, but to date a prophylaxis treatment is not recommended[24] (Table 1).

Fatigue

Fatigue is a common side effect of ADT which can worsen the quality of life of patients with PC reducing the patient's level of independence.[26] Fatigue may also be associated with depression.[95] The prevalence of fatigue varies from 66% to 77% and it is more common in patients treated with an LHRH agonist than with peripheral AR antagonists. Furthermore, a longer duration of hormone therapy is associated with a higher level of fatigue.[96]

ARPIs can cause worsening of fatigue in patients with PC and between ARPIs enzalutamide and apalutamide seem to determine a higher incidence of fatigue probably due to their ability to pass the blood–brain barrier. In a recent randomized trial in the mCRPC setting, enzalutamide showed an higher risk for fatigue compared to abiraterone.[97]

Physical exercise and dietary counselling are considered the best first-line treatment interventions in order to mitigate ADT-induced fatigue (Table 1). Many trials showed that various exercise regimens can reduce fatigue in men receiving ADT, and the benefit was greater for patients reporting highest levels of fatigue.[98] Current evidence for dietary

interventions to mitigate the side effects of ADT is limited, and there are no specific dietary recommendations. In a pilot randomized control trial, Baguley et al showed that the Mediterranean-style dietary pattern has the potential to improve quality of life in patients with PC treated with ADT, but further exploration of this diet is warranted in a larger powered sample size to consolidate these findings.[99] In general, patients starting hormone therapy should be advised to follow a healthy, varied and balanced diet according to WHO recommendations.

In patients treated with ARPI who experience fatigue that compromises the quality of life, a temporary withdrawal of ARPI may be considered, which generally results in improvement within a few days. Thereafter, ARPI treatment can be resumed at a reduced dose which generally results in a lower risk of fatigue.[25]

Anemia

Anemia is the most common haematological side effect in men receiving ADT. Testosterone promotes erythropoiesis by stimulating the differentiation of bone marrow erythroid stem cells and by increasing the renal production of erythropoietin.[100] Decreased haemoglobin levels can be seen in up to 90% of patients receiving ADT, but the prevalence of symptomatic anaemia is lower (0–37%).[101]

Anemia is usually normocytic and normochromic and asymptomatic. However, in a minority of patients, especially who had metastatic disease with bone marrow infiltration or who had cardiovascular comorbidities, anaemia can become severe and may be associated with increased life-threatening complications.[101]

The hemoglobin level should be tested before starting the ADT and during the treatment period. If anemia is found, a dosage of vitamin B12, folate or iron should be performed and supplementary therapy should be started in case of deficiency[24] (Table 1).

Sexual Disfunction

ADT impact on multiple domains of sexual function that may deeply affect the quality of life of patients with PC. ADT can cause a reduction in penis length and testicular atrophy which combined with alterations in weight, muscle mass, and gynecomastia, may have a detrimental impact on self-perceived body image leading to poor sexual function and decreased partner intimacy.[102,104] The association between ADT, reduced libido and erectile disfunction is well known. A recent metanalyses showed that ADT resulted in a five to sixfold increased risk of reduced libido and in a threefold increased risk of erectile disfunction.[102]

In a cohort study of 250 patients undergoing intermittent ADT (LHRH agonist + antiandrogen), it was demonstrated a worsening of the sexual activity.[104] From a baseline of 46% of patients reporting sexual activity, at 9 months only 13% of the men did so, and 10% reported moderate to high libido vs an initial 63%. The proportion of men feeling less masculine increased to 50% as a result of hormonal treatment, against 26% at baseline. During the off phase of the intermittent treatment, 52% of previously sexually active men resumed sexual activity. Levels of libido, masculinity and sexual activity recovered but not to baseline levels, thus showing that the side effects are only partially reversible in the majority of patients and should therefore be addressed both in patient in treatment and survivors.[104]

Before starting ADT patients should be adequately informed about the possible side effects on sexual activity. Referrals to psychosocial support groups and/or sex therapists should be offered to interested patients (Table 1). Erectile dysfunction may be treated with various interventions, including phosphodiesterase inhibitors; however, treatment efficacy may be poor without adequate mental and physical arousal.[102] Intermittent ADT has been shown to improve sexual function and should be considered in appropriate patients. Hussain et al showed that patients with mHSPC treated with intermittent ADT had a better erectile function at month 3 ($p<0.001$) than patients treated with continuous ADT.[70]

Renal Toxicity

The use of ADT may increase the risk of acute kidney injury (AKI).[103] In a study of more than 10,000 patients, ADT was associated with an increased risk of AKI when compared with never use (odds ratio 2.48, 95% CI 1.61–3.82).[103] Testosterone appears to protect the kidneys by inducing vasodilation in the renal vessels, thus the use of ADT might increase the risk of damage to the glomerulus. Furthermore, ADT-induced hypogonadism leads to estrogen deficiency

and estrogens play a protective role in ischemic renal injury by reducing glomerular endothelial permeability.[103,105] Adding ARPIs to ADT does not appear to increase renal toxicity.[105]

An early recognition of renal impairment represents an important aspect to minimize the risk of renal injury. This can be accomplished by a routine use of glomerular filtration rate (eGFR) estimation rather than serum creatinine value alone (which may be in the normal range in older patients or those with muscle wasting) which should be evaluated before starting hormone therapy and during the treatment period.[105]

ARPI-Specific Adverse Events

As previously discussed, ARPIs can worsen some of the adverse events induced by ADT. However, ARPI-specific adverse events do exist and they differ among the various ARPIs.

Abiraterone

Abiraterone acetate is a steroidal antiandrogen which acts via selective and irreversible inhibition of cytochrome P450 17A1 (CYP17A1) and is used at a dosage of 1000mg/day.[107] CYP17A1 is a key enzyme in cortisol and androgen biosynthesis.[10] The inhibition of glucocorticoids synthesis, causing a compensatory increase in the ACTH and consequently an excess of mineralocorticoids which can cause hypokalemia, hypertension, peripheral edema and congestive heart failure. Therefore, glucocorticoid replacement therapy with low-dose prednisone (5–10mg/day) is required to minimize the incidence of mineralocorticoid excess symptoms[106] (Table 2). In the pivotal study COU-AA-301 abiraterone was used in patients with mCRPC previously treated with docetaxel.[14] In this trial 17% of patients treated with abiraterone experienced hypokalaemia, 10% developed hypertension, while fluid retention and edema and cardiac disorders occurred in 31% and 13%, respectively.[14] Similar results were achieved in the COU-AA-302 study where abiraterone was used in patients who had not received prior docetaxel treatment.[15] In this study, hypokalaemia occurred in 17% of patients, hypertension in 22% while fluid retention or

Table 2 Summary of ARPI-Specific Adverse Events and Their Management

ARPI	Specific Adverse Event	Physiopathology	Managemnt
Abiraterone	• Hypokalemia • Hypertension • Peripheral edema • Congestive heart fail • Liver function impairment	• Inhibition of CYP17A1	1. Glucocorticoid replacement therapy with low-dose prednisone (5–10mg/day) 2. Monitor potassium and liver function values during treatment 3. Carefully consider the use of abiraterone in patients with cardiovascular comorbidities 4. Reduce the dose or discontinue treatment in case of severe adverse events
Enzalutamide	• Hypertension • Fatigue • Seizures	• Passage through the blood–brain barrier • Off-target activity to induce inhibition of GABA-A receptors	1. Avoid the use of enzalutamide in patients with a predisposition to develop seizures 2. Reduce the dose or discontinue treatment in case of severe adverse events
Apalutamide	• Hypertension • Fatigue • Seizures • Hypothyroidism • Skin rash	• Passage through the blood–brain barrier • Off-target activity to induce inhibition of GABA-A receptors • Interacts with thyroxine and levothyroxine	1. Avoid the use of apalutamide in patients with a predisposition to develop seizures 2. Corticosteroids and oral antihistamines for skin rash 3. Start or optimize treatment with levothyroxine 4. Reduce the dose or discontinue treatment in case of severe adverse events
Darolutamide	• No increase in adverse events compared to placebo	• Less ability to pass the blood–brain barrier	1. Reduce the dose or discontinue treatment in case of severe adverse events

Abbreviations: ADT, androgen deprivation therapy; ARPI, androgen receptor pathway inhibitors; BMI, body mass index; BPA, bisphosphonates; BMD, bone mineral density; ECG, electrocardiogram; GABA-A, gamma-aminobutyric acid-A; Hb, hemoglobin; LHRH, luteinizing hormone releasing hormone; mCRPC, metastatic castration-resistant prostate cancer.

edema and cardiac disorder in 28% and 19% of patients.[105] Hypertension and hypokalemia were the main adverse events induced by abiraterone in the LATITUDE trial in which abiraterone was used in patients with mHSPC (37% and 20% respectively).[20] In particular, grade 3 hypertension and hypokalaemia occurred in 20% and 11% of cases. 12% of the patients instead developed cardiac disorders.[20] Finally, in the STAMPEDE study, 5% and 1% of patients with mHSPC developed grade 3 hypertension and hypokalaemia, respectively, while grade 3 cardiovascular changes occurred in 10% of patients.[10] It is important to underline that while in the studies in the mCRPC setting (COU-AA-301 and COU-AA-302) patients received 10mg/day of prednisone in addition to abiraterone, in the studies in the mHSPC setting (LATITUDE and STAMPEDE) the patients randomized in the abiraterone arm they were concomitantly treated with 5mg/day of prednisone/prednisolone.[10,14,15,20]

Abiraterone can also rarely cause liver function impairment with an increase in liver enzymes.[25] In the previously mentioned studies 10–16% of patients experienced an increase in liver enzymes of which in 3–6% of grade ≥ 3.[10,14,15,20] Currently, the mechanisms of liver function test increase on abiraterone are unknown. In patients with impaired hepatic function abiraterone should be considered carefully. During treatment follow-up, serum potassium, transaminase and bilirubin levels should be evaluated every 2 weeks for the first 3 months and thereafter monthly.[107] In case of severe adverse events abiraterone should be discontinued. Treatment can be re-initiated at a reduced dose of 500mg/day once toxicity resolves or improves.[107]

Enzalutamide

Enzalutamide is a non-steroidal AR inhibitor and is administered at a dosage of 160mg/day.[52] The most frequently reported adverse events associated with enzalutamide are hypertension and fatigue. Fatigue was the most frequent adverse event in patients with mCRPC treated with enzalutamide in the AFFIRM and PREVAIL study (34–36% of which 2–6% grade > 3), while hypertension occurred in approximately 13% of cases of which in 7% grade≥ 3 in these studies.[16,17] Similar results occurred in the PROSPER study, in which enzalutamide caused fatigue and hypertension in approximately 33% and 12% of patients in patients with nmCRPC.[18] Fatigue and hypertension occurred less frequently in patients with mHSPC treated with enzalutamide in the ARCHES and ENZAMET studies (6–19.6% and 8% respectively).[12,21]

Furthermore, enzalutamide can induce seizures due to their off-target activity of inducing an inhibition of GABA-A receptors, therefore enzalutamide should be avoided in patients with a predisposition to develop seizures.[25] In the previously mentioned studies in which patients with a history of seizure or a condition that may confer a predisposition to seizure were excluded, seizure occurred in <1% of patients.[12,16–18,21]

In case of serious adverse event, it must be suspended and possibly restarted at a lower dosage of 80mg/day in case of improvement or resolution of toxicity. If the dosage of 80mg/day is well tolerated by the patient, it is possible to increase the dosage to 120mg/day[52] (Table 2).

Apalutamide

Apalutamide is a non-steroidal AR inhibitor with a chemical structure similar to that of enzalutamide which is administered at a dosage of 240 mg/day.[108] Like enzalutamide also apalutamide can cause fatigue, hypertension and risk of seizures. In the SPARTAN study which enrolled patients with nmCRPC, 30.4% of patients treated with apalutamide developed fatigue while hypertension occurred in 24.8% of cases (14.3% grade≥ 3).[19] In this study, 2 patients (0.2%) experienced seizure.[19] Fatigue and hypertension occurred less frequently in mHSPC patients treated with apalutamide in the TITAN study (19.7% and 17.7% respectively).[11] Also in these studies, patients with a history of or predisposition to seizure could not be enrolled.[11,19]

Specific adverse effects of apalutamide are hypothyroidism and skin rash most commonly in the form of macular or maculo-papular lesions.[25] In the previously mentioned studies, hypothyroidism occurred in 6.5–8.1% of patients, while 23.8–27.1% of patients experienced a skin rash of which in 5.2–6.3% grade≥ 3.[11,19]

In patients receiving apalutamide, clinicians should evaluate thyroid function at the beginning and during treatment. The management of hypothyroidism in most cases required only an increase in levothyroxine dose or a de novo initiation of thyroid replacement therapy (Table 2). In the case of skin rash, treatment options include topical corticosteroids, oral antihistamines, or even systematic corticosteroids, depending on the extent and severity of the skin rash.[25] In patients

with severe adverse reactions, apalutamide should be withheld to mitigate side effects and reinitiated at the reduced dose upon resolution of symptoms.[25] Generally the therapy is restarted with a halved dose (120 mg/day) and if well tolerated the dose can be increased up to 180 mg/day.[108]

Darolutamide

Darolutamide is a non-steroidal AR inhibitor with a distinct chemical structure compared to apalutamide and enzalutamide which determines a reduced penetration of the blood–brain barrier and consequently a reduction of central nervous system side effects, such as fatigue, cognitive impairment and seizures. Darolutamide is administered at a dosage of 600 mg x2/day.[109] Clinical trials evaluating darolutamide did not show an increase in adverse events compared to placebo.[13] In patients with nmCRPC treated with darolutamide in the ARAMIS study, 12.1% of patients experienced fatigue (versus 8.7% of patients treated with placebo) and 6.6% of patients developed hypertension (versus 5.2% of patients treated with placebo).[13] Similar results occurred in the ARASENS trial in which the addition of darolutamide to the ADT + docetaxel combination did not result in an increase in side effects compared to placebo.[110]

Although no clear recommendations exist, in patients presenting with serious or intolerable adverse reactions the darolutamide dosage should be reduced to half dose (600 mg/day) and increased up to 900 mg/day if well tolerated.[109] (Table 2).

Conclusions

Hormonal therapies represent the cornerstone of the systemic treatment of PC.[3] Although these are generally well-tolerated therapies, they can cause adverse events that can worsen the quality of life of patients and consequently compromise treatment compliance. The increasing use of ARPIs in earlier stages of the disease will lead to an increased exposure of patients to these treatments and consequently to their possible adverse events. Several studies have documented an important reduction in quality of life in patients with PC treated with hormonal therapies.[26,111] A study including patients treated with ADT showed a statistically significant reduction in different quality of life items, such as mental health and general health, energy and concern regarding body image.[111] Fatigue and depression induced by ADT can interfere with cognitive function, producing a significant reduction in the quality of life of patients with prostate cancer.[26]

Clinicians caring for patients with PC should adequately inform patients of the possibility of developing these adverse events and possible treatment options to mitigate them. Furthermore, patients starting hormone treatment should be carefully followed over time to diagnose and treat any adverse events early. It is useful to discuss with other specialists (eg cardiologist, psychiatrist or geriatrician) before starting hormone therapy in patients at increased risk of developing adverse events and the choice of treatment should take into account their evaluation. Moreover, in the management of adverse events caused by hormonal therapies it would be useful to perform a multidisciplinary evaluation by discussing with specific specialists. Furthermore, the use of specific validated questionnaires to assess treatment toxicities and to monitor patients' quality of life should be implemented in clinical practice. Since we do not always have treatments available to improve the adverse events induced by hormonal therapies, the most studied therapeutic strategy is represented by the use of intermittent hormonal therapy. Several studies have demonstrated that intermittent ADT is associated with a reduced rate of side-effects and better quality of life than continuous ADT.[70,87,93,104] However none of the trials that addressed intermittent versus continuous ADT in mHSPC patients showed a survival benefit but there was a constant trend towards improved OS with continuous ADT although most of these studies were non-inferiority trials.[70,87,93,104] On the other hand, there is no evidence on intermittent hormonal therapy in patients with mHSPC treated with ADT + ARPI since all the trials that evaluated this combination did not provide for the use of intermittent therapy. It is possible that selected patients with mHSPC (eg patients with low disease burden who reach undetectable PSA values within a few months after starting hormonal therapy) may benefit from intermittent therapy in terms of reduction of side effects and improvement of quality of life without compromising the efficacy of the therapy. Therefore, future studies evaluating a de-intensification of treatments in patients with mHSPC are needed.

Also another possible approach to reduce the toxicity of hormone therapy is to postpone its start. In a prospective, randomized phase 2 study, Ost et al showed that metastasis-directed therapy (MDT) prolongs ADT free-survival in

oligorecurrent PC patients (up to a maximum of 3 metastases) compared to observation (HR, 0.60; 80% CI, 0.40–0.90; log-rank p=0.11) with no grade 2 to 5 toxicity.[112] In another phase 2 study, Philips et al showed that MDT improved median progression-free survival compared to observation (HR 0.30; 95% CI, 0.11–0.81; p=0.002) in oligorecurrent mHSPC patients (1–3 metastases) with no toxic effects of grade 3 or greater.[113] Finally, the long-term results of these 2 studies confirmed the benefit of MDT in patients with oligorecurrent PC.[114] The results of MDT are therefore promising in order to postpone the start of a systemic therapy and consequently its side effects. However, it must be emphasized that the control arm of the 2 studies was represented by observation which does not represent the standard of care of patients with metastatic PC. Future studies evaluating MDT vs standard of care systemic therapies in patients with mHSPC are needed.

Finally, future studies are needed to investigate some poorly studied adverse events of hormone therapies, such as cognitive alterations and to identify new therapeutic options to improve the quality of life of patients with PC. In fact, although several studies are ongoing that are evaluating the efficacy of new therapeutic options in patients with PC, there are few studies that are focusing on the management of treatment toxicities and on identifying strategies that can improve the quality of life of these patients.

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