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REVIEW ARTICLE

Prostate Cancer and Androgen Deprivation Therapy: Metabolic, Cardiovascular and Psychological Side Effects

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Abbreviations:
ADT: androgen deprivation therapy,
BMI: body mass index,
CV: cardiovascular,
GnRH: gonadotropin releasing hormone,
HDL: high-density lipoprotein,
LDL: low-density lipoprotein,
LHRH: luteinizing hormone releasing hormone,
MS: metabolic syndrome,
PCa: prostate cancer

ABSTRACT

Exposure to androgen deprivation therapy (ADT) by prostate cancer (PCa) patients is increasing, either in early-stage and in metastatic disease. Frequently, ADT becomes a long-term treatment, lasting even more than 10 years, starting with gonadotropin releasing hormone (GnRH) agonists or antagonists, until the newest hormonal treatments as Abiraterone and Enzalutamide. As a consequence, ADT related adverse events occurred. We reviewed the medical literature using Pubmed search terms "prostate cancer", "androgen deprivation", "metabolic syndrome", "cardiovascular diseases" and "psychological assessment". The search was limited to manuscripts published in English language between 1999 and 2016, preferring more recent review articles. Metabolic syndrome, diabetes and cardiovascular diseases, rather than PCa itself, are the most common causes of mortality, particularly in early stage PCa patients. All these adverse eff ects synergistically increase morbidity in patients taking ADT. Psychological-cognitive implications emerging during ADT result in a signifi cant reduction of health-related quality of life of PCa patients. ADT is associated with several adverse events, which physicians andpatients should evaluate when recommending ADT. Multidisciplinary approach, with diff erent clinicians such as Urologist, Radiotherapist, Oncologist, Endocrinologist, Cardiologist, Psychologist, is mandatory for the suitable clinical management of patients with PCa submitted to ADT.

Alessandra Mosca

INTRODUCTION

Prostate cancer (PCa) is the most commonly diagnosed tumor in men, either in US where it represents the second leading cause of cancer-related death, and in Europe, where it is the third cause.[1]

Over the years, the progressive increase of PCa incidence, which is expected to be even higher in the next future, has been due to the improvement either in diagnostic techniques and in median life expectancy. Alongside, PCa specific survival is rising, with 98.8% contemporary 5-year relative survival for men with all stages of Pca.[1-3]

For localized/locally advanced and metastatic PCa, the standard treatment is androgen deprivation therapy

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(ADT), obtained through bilateral orchiectomy (surgical castration) or through medical castration by LHRH-agonists + anti-androgens or by LHRH-antagonists.[4-6] Currently, standard duration of ADT is not yet established, ranging from a few months up to 3 years, depending on different clinical setting.[7] As ADT prescription increased during the last years, across all ages, disease stages and tumor grades, PCa patients exposure to long-term ADT rised, sometimes lasting more than 10 years, with related several toxicities.[8,9]

More than 80% of PCa occurred in men >65 years old, who often present formerly many comorbidities, such diabetes, dyslipidemia, cardiovascular illness, initial cognitive disorders.[10,11] As a consequence, nowadays PCa patients become much older due to longer life expectancy and to improved therapeutic outcomes, but carrying a high risk to develope both comorbidities age-related and toxicities linked with long-term ADT, with subsequent impact on metabolic and cardiovascular systems, psychological assessment and quality of life.

This review will summarize recent issues concerning the most relevant side effects derived from ADT in PCa patients, such as metabolic syndrome, cardiovascular diseases and psychological changes, highlighting the need to approach PCa patients with a multidisciplinary attitude.

METHODS

Data for this review were identified on Medline using the search terms "prostate cancer", "androgen deprivation", "metabolic syndrome", "cardiovascular diseases" and "psychological assessment". From the references obtained, selection was made based on clinical relevance and importance of the article. Other references were identified from the reference list of retrieved articles. The search was limited to manuscripts published in English language between 1999 and 2016, preferring more recent review articles.

Prostate Cancer, Androgen Deprivation and Metabolic Syndrome

Metabolic syndrome during ADT for PCa

ADT in PCa patients may lead to metabolic alterations and unfavorable changes in body composition, such as weight gain, loss of muscle mass, increased fat mass, and decreased muscle strength.

In contrast with classic metabolic syndrome, ADT-related metabolic syndrome (MS) comprehends: 1) increased waist circumference, with subcutaneous fat accumulation and gain in fat and loss of lean body mass: this was observed in 14-70% of patients submitted to LHRH-agonists; 2) increased triglycerides, total cholesterol, HDL and LDL; 3) increased adiponectin; 4) increased fasting insulin with concomitant decreased insulin sensitivity.[12,13] As a consequence, the risk of type 2 diabetes mellitus and cardiovascular events increases.[12,14,15]

Not only prolonged (>6 months) but even short-term (12 weeks) ADT significantly increases fat mass and decreases insulin sensitivity in PCa patients.[16] This is clinically relevant, as retrospective data showed that hyperinsulinemia and obesity are crucial promoters of PCa progression during ADT, suggesting that MS might represent a risk factor for earlier development of castration-resistant Pca.[12,17,18]

In parallel, the loss of strenght and quality of skeletal muscle mass, known as "sarcopenia", arising in approximately 20% of patients during ADT, is associated with the loss of lean body mass greater than 5%,[19] causing a great change in body composition of PCa patients.

Concerning the newest hormonal therapies such as Abiraterone,[20] which blocks the androgen synthesis in adrenal glands through CYP17 inhibition, and Enzalutamide,[21] which is a potent androgen-receptor-signaling inhibitor, very limited data are now available in relation with MS, as the use of the two drugs in daily clinical practice is very recent.

Metabolic syndrome and PCa without ADT

Metabolic alterations seem to have some impact even in PCa patients not submitted to ADT.

Two cross-sectional studies showed that preexisting MS in men might be associated with poor outcomes, such as more advanced and high-grade disease, when they have diagnosis of PCa. Nevertheless, this negative association needs to be confirmed in prospective trials.[12,22,23]

Retrospective studies highlighted that men with coexistent MS and newly diagnosed PCa, after a definitive surgery or radiation therapy for localized disease, they might have a higher risk of PSA recurrence and metastases appearance. However, these data could be also related to the greater technical difficulty to achieve a local control of disease in obese patients.[12]

In the effort to hypothesize the link between preexisting MS and PCa development or worsening in the absence of ADT, it has been observed that MS is associated with a chronic, low grade inflammation state, with elevated levels of C-Reactive Protein and proinflammatory cytokines such as TNF-alfa, IL-8, IL-6 and IL-1beta,[24] which are well known growth factors potentially able to favour PCa progression.

Considering correlation between MS and PCa-specific mortality, data are debatable. Some studies underlined the direct correlation among obesity, MS, and an increased risk of PCa-specific mortality in the absence of ADT (i.e. non-metastatic castration-naive PCa patients).[12,17,25,26] On the contrary, a retrospective analysis of 1208 metastatic, castration-resistant PCa patients, with progressive disease during ADT, showed that obesity is associated with a decreased risk of PCa–specific mortality compared to normal body mass index (BMI).[27] Notably, results of these two studies can not be directly compared, they could only be considered as hypothesis generating, as the two study populations are completely different (non-metastatic castration-naive versus metastatic castration-resistant PCa patients), with distinct risks of PCa–specific mortality.

The hypothesized association between preexisting MS and PCa development is controversial. Two prospective studies showed a positive association between earlier MS and Pca,[28,29] suggesting that the combination of 2 or 3 MS factors might be predictive of PCa.[29] In contrast, other data demonstrated a negative association between prior MS and diagnosis of PCa, observing that men with MS had a significantly lower incidence of Pca.[30-32]

Finally, metabolic syndrome together with diabetes and/or cardiovascular diseases, rather than PCa itself, are the most common causes of mortality in PCa patients, in particular in men with early stage PCa without ADT.[33] Anyway, all these diseases synergistically increase morbidity in PCa patients submitted to ADT.[13]

Prostate Cancer, Androgen Deprivation and Cardiovascular Diseases

While the profound impact of ADT on metabolic changes has been stated, the real influence on cardiovascular (CV) events and morbidity remains still controversial.

It has been theorized that LHRH-agonists could be responsible for CV toxicity on heart and blood vessels through either an indirect and a direct mechanism.

According to the indirect mechanism, metabolic complications derived from ADT, such as increased body weight, insuline resistance, dyslipidemia and hypogonadism, may accelerate the atherosclerosis process and lead to increased risk of CV events. Furthermore, as testosterone acts directly on heart and blood vessels as a potent coronary vasodilator and has an important role in arterial stiffness,[7,34,35] androgen deficiency ADT-related contributes to increase the arterial wall thickness and the endothelial dysfunction, with subsequent increased vasoconstriction, arterial sclerosis, oxidative stress, thrombosis, and possible contribution to initiate early stage of atherosclerosis, to propagate and enlarge the lesions, and to modify the late stage of plaque rupture, causing serious CV diseases.[7,36,37]

In relation with the direct mechanism of LHRH-agonists on CV toxicity, some studies hypothesized a direct effect of Gonadotropin Releasing Hormone (GnRH) agonists on cardiomyocytes, leading to a negative influence on cardiac function, as GnRH agonists could regulate cardiac contractility and intracellular calcium ions concentration. Indeed, GnRH agonists could cause arrythmias and possible QT interval prolongation.[7,37,38]

Several cohort studies analyzed the correlation between ADT and increased incidence of CV diseases. Some but not all studies confirmed an association between ADT and a greater risk of CV events. Keating et al,[14] in a retrospective study of more than 70.000 PCa patients, showed that men who received GnRH agonists had a higher incidence of coronary heart disease, myocardial infarction, sudden cardiac death, while men who underwent bilateral orchiectomy had not.[2] Tsai et al. retrospectively analysed more than 3.200 PCa patients, underlining an increased risk of CV mortality with neoadjuvant (before radical prostatectomy or radioterapy) or adjuvant (after radical prostatectomy or radioterapy) ADT.[39] Saigal et al, in retrospective data of more than 22.800 PCa patients, demostrated that ADT caused a 20% increased risk of serious CV morbidity at 1 year.[40] A recent meta-analyses on associations between types of ADT and non-fatal and fatal CV disease outcomes, based upon observational studies, showed a consistent positive association between ADT and the risk of CV diseases.[41]

In contrast, several studies, including randomized controlled trials, suggested no relationship between ADT and CV events.[7]

On the basis of above listed and other information, the US Food and Drug Administration, the American Heart Association, the American Cancer Society, the American Urological Association, and the American Society of Radiation Oncology warned about the potential relationship between ADT and CV events.[7]

Regarding the association between CV morbidity and ADT duration,[7] as well the potential decreased risk of CV events during intermittent, instead of continuous, ADT, data are still not conclusive.[8,9,42]

Concerning ADT with GnRH antagonists, very few data are available until now. According to the phase III comparative study, Degarelix apparently caused lower incidence of ischemic heart disease and supraventricular arrhytmia

than Leuprolide.[43] In contrast, other two studies showed similar CV safety profiles for Degarelix and Leuprolide in PCa patients.[44,45]

Very few available data about Abiraterone and Enzalutamide suggest a good safety profile regarding CV events.[46,47]

In conclusion, as ADT could potentially increase the CV risk factors or pre-existing CV diseases, it is advisable to check PCa patients for metabolic and CV effects before starting ADT and periodically during hormone-therapy, encouraging patients to follow a healthy lifestyle, with balanced diet and regular physical activity.

Prostate Cancer, Androgen Deprivation and Psychological Disorders

Aside from the physical consequences, there is increasing recognition of concurrent adverse psychological effects derived from ADT.[48-50] Men submitted to ADT describe emotional lability and psychological changes, including depressed mood.[51] ADT may also affect the brain, as it expresses a widespread distribution of both estrogen and testosterone receptors, therefore subsequent minor cognitive changes could appear already 3-12 months after ADT start.[11,52-55] Serum testosterone reduction may alter serotonin neurotransmission,[56] thus negatively affecting mood, as demonstrated in preclinical setting.[57] Reduced testosterone levels may contribute to decrease cerebral perfusion in memory, reasoning, judgement and emotion areas of the brain, leading to a mental deterioration.[58-60] Furthermore, low circulating testosterone levels correlate with reduced sleep efficiency, with altered rapid eye movement (REM) sleep latency.[61] Emotional lability reported by patients submitted to LHRH agonists includes anger, pessimism, bitterness, irritability.[13] Few studies, either in nonmetastatic and in metastatic PCa patients, attempted to define the correlation between ADT and depression, but the impact of ADT on depression incidence and development still remains unclear.[11,50,62-67] Supporting a link between ADT and mood changes, previous studies observed an increase in depression and anxiety during androgen suppression therapy.[62,68,69] Furthermore, Saini et al demonstrated that adjuvant ADT was associated with depression in nonmetastatic PCa patients,[66] while Chipperfield et al showed that the likelihood of clinically significant anxiety and depression increased with the number of comorbidities.[50] A recent longitudinal case-control study in PCa patients receiving ADT (61 patients) or not (61 patients) demonstrated that the rates of clinically-significant depressive symptomatology increased significantly six months later ADT start.[70] Very recently, Sharp et al investigated the associations between PCa symptoms and psychological wellbeing, administering postal questionnaires (EORTC QLQ-C30, QLQ-PR25, DASS-21) among 3348 men with PCa diagnosed 2-18 years previously. They observed that 17%, 16% and 11% of PCa patients scored in the range for depression, anxiety and distress, respectively. Furthermore, in multivariate models they found out that: 1) risk of depression was significantly higher in PCa patients with higher urinary and ADT-related symptoms, and higher fatigue, insomnia and financial difficulties scores; 2) risk of anxiety was higher inPCa patients with higher scores for urinary, bowel and ADT-related symptoms and fatigue, dyspnoea and financial difficulties; 3) risk of distress was positively associated with urinary, bowel and ADT-related symptoms, fatigue, insomnia and financial difficulties.[71]

By contrast, other recent studies did not find any statistically significant association between ADT and depression. Timilshina et al stated that 12 months ADT was not associated with worsening depressive symptoms in a secondary analysis from a prospective cohort study with 257 nonmetastatic PCa patients.[11] Hervouet et al showed that ADT is associated with increased, but not statistically significant, depressive symptoms in nonmetastatic PCa patients.[67]

Even data related to cognitive changes are conflicting. Some studies demonstrated decline in spatial performance, memory and executive functioning, other data failed to show the same changes, while further authors revealed an improvement in cognitive abilities during ADT.[13] As Alibhai et al suggested, these opposing results of literature data might derive from variability in cognitive-psychological tests used, duration and type of ADT, patient demographics, disease characteristics and control group.[72]

Overall, when psychological-cognitive problems occur during ADT, they result in a significant reduction of health-related quality of life of PCa patients. With the need to identify effective interventions, some authors underlined the potential utility of physical activity for nonmetastatic PCa patients undergoing ADT, suggesting that a home-based exercise program[73] or a moderate weekly physical activity[50,74,75] may improve quality of life and psychosocial well-being in this patient population. Furthermore, other authors recommended psychological support either to PCa patients and to their partners.[76,77]

Data concerning Abiraterone and Enzalutamide and psycosocial implications are not yet available.

CONCLUSIONS

In recent years, PCa survivors are increasing, now representing a large and growing population of potential vulnerable older men due to ADT-related toxicity.

ADT, particularly with GnRH agonists, is associated with several metabolic changes, increased risk of diabetes and CV diseases, and psychosocial complications. Very limited data are available in relation with the newest hormonal therapies, such as Abiraterone and Enzalutamide.

Physicians and patients should consider every particular side effect when making treatment decisions concerning ADT. Clinicians should educate patients about these risks, suggest lifestyle modifications when necessary, screen for prediabetes/diabetes and lipid assessment, and manage the adverse events with the proper treatment.

In conclusion, it is essential to coordinate the care of PCa patients submitted to ADT by different clinicians, such as Urologist, Radiotherapist, Oncologist, Endocrinologist, Cardiologist, equally involved in the multidisciplinary clinical management.

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