

CARDIOVASCULAR RISK ASSOCIATED WITH ANDROGEN DEPRIVATION THERAPY IN ADVANCED PROSTATE CANCER

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ABSTRACT

Cancer is a lethal disease that is the second leading cause of mortality in the world. According to statistics, prostate cancer is one of the most common types among men. Male hormone androgens, particularly testosterone, are required for normal growth and functioning of the prostate. In prostate cancer, activation of the androgen receptor promotes the growth of cancer cells. The goal of hormonal therapy or androgen deprivation therapy (ADT) is to reduce levels of such male hormones in the body or prevent them from stimulating cancer cells. There are many issues that have to be considered before initiation of hormonal therapy which are necessary to be aware of for its prevention and the management in routine clinical practices. In this review article, we emphasize on cardiovascular complications following ADT and certain treatment measures.

Keywords: Prostate cancer, Androgen deprivation therapy, Testosterone, Cardiovascular complications, Gonadotropin-releasing hormone agonist.

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INTRODUCTION

Although prostate cancer is a global health problem, it is a common cancer in men and on the Asian continent it is only now found to be increasing rapidly [1-4]. Changing lifestyles may remain one responsible factor for this [5]. The global incidence is 1:52 in men aged 50–59 years, and nearly 60% in men aged 60 and up [6]. In India, there is a significant variation in incidence, disease characteristics and mortality rate, with the incidence being considerably higher in the urban population. Localized prostate cancer can be controlled by surgery or radiation therapy [7-9], but advanced prostate cancer was not curable. Treatment for advanced prostate cancer was mainly palliative care, which provides symptom relief and maintains the quality of life. However, now the advancement of androgen deprivation therapy (ADT) is a key therapeutic intervention in men with advanced prostate cancer [10]. Hormone therapy has been shown to enhance clinical and pathological characteristics in early prostate cancer patients [11]. The mainstay of treatment for metastatic prostate cancer is the administration of a gonadotropin-releasing hormone (GnRH) agonist on a long-term basis [12]. ADT is the use of an orchiectomy or a luteinizing hormone releasing hormone (LHRH) agonist to manipulate the hypothalamic-pituitary-gonadal axis to attain castrate levels of testosterone [13,14]. ADT causes adverse effects including bone loss, metabolic changes, gynecomastia, muscle loss, hot flash and cardiovascular (CV) complications [15]. We conducted a review that focuses predominantly on the CV complications of ADT. In 2006, awareness of the problem began with the publication of an observational surveillance, epidemiology and end results (SEER)-Medicare study by Keating *et al.* [16]. The US Food and Drug Administration issued a drug safety communication in 2010 requiring manufacturers of GnRH agonists to change their labeling to include a warning about “increased risk of diabetes and certain CV diseases (CVDs) (heart attack, sudden cardiac death, and stroke)” [17]. Following that, various reviews on ADT and its negative effects were released. In this narrative review we aim to improve awareness of the relationship between long-term Androgen Deprivation associated with increased risk of CV complications along with the management measures for patients developing CV complications.

PATHOGENESIS

Testosterone is the major male hormone primarily produced by testes [18,19]. LHRH, also known as GnRH controls this process by

regulating Luteinizing hormone production by the anterior pituitary gland. Only 90% of testosterone is produced by the testes, with the remaining 10% derived from adrenal steroid synthesis. The weak androgens dehydroepiandrosterone and androstenedione secreted by the adrenal glands are converted to testosterone in peripheral tissues and prostate gland [20]. Androgens are essential for the development, growth and functioning of the prostate. Testosterone diffuses along a concentration gradient into the prostate. Five- α -reductase reduces Testosterone to dihydrotestosterone (DHT). DHT is the primary androgen that controls cell division in the prostate gland. DHT possesses higher affinity towards prostate tissues and is twice as potent as testosterone for prostate growth stimulation [21]. The beneficial clinical effects of suppressing serum testosterone levels in men with advanced prostate cancer was first found by Huggins and Hodges in the year 1941, for which they received the Nobel prize in the year 1966 [9]. In addition, ADT is universally accepted as a treatment for symptomatic metastatic prostate cancer. CV effects of androgens in normal/pathological conditions can lead to either positive or negative effects. Androgens play a role in the modulation of vascular endothelium tone, proliferation, motility, adhesion, and anti-thrombotic characteristics. These hormones equally participate in important pathogenic mechanisms such as vascular inflammation and these structural changes contribute to plaque and thrombus formation in the vessels [22,23]. Another study reveals that loss of androgens in men leads to an increase in aortic stiffness and serum insulin, which contributes to an increase in CV risk [24]. The alleged mechanism underlying the association of ADT with elevated risk of CV events in patients with prostate cancer is hypothetical. However, it's thought to be linked to ADT-induced metabolic and immunomodulatory alterations that destabilize pre-existing atherosclerotic plaque in people who have already had a heart attack or stroke, potentially accelerating the progression of atherosclerosis. One possibility is that potential cardio-protection provided by testosterone is disrupted by ADT. Another theory is that circulating T lymphocytes that can express the GnRH receptor become activated and penetrate atherosclerotic plaque, disrupting the fibrous cap and destabilizing the plaque [25]. The causes of the inequalities are unknown; however, they may be related to vascular endothelial heterogeneity and androgen-specific effects on men and women [22]. Reduction of androgen levels may contribute to risk factors for CVDs such as obesity, hyperlipoproteinemia, hypertension and diabetes mellitus. A randomized control trial by Smith *et al.* found

that administration of GnRH agonists such as Leuprolide causes body composition changes associated with CV risk, including increased body fat (9.4–11.2%), decreased lean muscle mass (2.7–3.6%), hyperlipoproteinemia, especially increased levels of high-density lipoprotein (HDL) [26]. Hormonal agents used in prostate cancer are given in Table 1 [27,28].

ADT ASSOCIATED CV RISK

CVD remains the leading cause of death worldwide, with over 17 million deaths per year and a projected increase to over 23.5 million by 2030 is expected [29]. The majority of evidence establishing a link between ADT and CVD is observational in nature. Even short-term administration of ADT might cause osteoporosis, obesity, sarcopenia, lipid changes, insulin resistance, and an elevated risk of diabetes and CV morbidity, to name a few [30]. An Italian real-world analysis shows that the majority of patients received GnRH agonists rather than a GnRH antagonist [31]. SEER Medicare data for this analysis cohort included 73,196 men with locoregional prostate cancer. In men, GnRH agonists are linked to an increased risk of diabetes, coronary heart disease, myocardial infarction (MI), and sudden cardiac death, while orchiectomy was not linked to any of these events [16]. In a univariate analysis of a population-based study, the prevalence of two CVD risk factors, hypertension and diabetes, was found to be higher in the ADT group than in men not receiving ADT. Those who had ADT after being newly diagnosed with prostate cancer had a 20% higher risk of significant CVD morbidity than men who did not receive ADT. Given the contribution of CVD to mortality in men with low risk or intermediate risk disease, those patients who undergo adjuvant or neoadjuvant ADT for even a brief duration may actually experience decreased survival as a result of the intervention [21]. According to the Cancer of the Prostate Strategic Urologic Research Endeavor database, this study looked at data from 3262 individuals who had a radical prostatectomy and 1630 individuals who had localized prostate cancer and were treated with external beam radiation therapy, brachytherapy or cryotherapy. After correcting for age (a continuous variable) and the presence of baseline CVD risk factors, competing risk regression analyses were conducted to see if using ADT was related to a shorter time to death due to CV causes. According to the findings, ADT use was linked to a statistically significant increase in the risk of death from CVD-related causes in patients managed with radical prostatectomy. ADT use was coupled with a significant cumulative incidence of untimely onset of fatal MI and death due to CVD causes among patients aged 65 and older who underwent brachytherapy, external beam radiation treatment or cryotherapy, although the difference did not attain statistical significance [32,33]. Tsai *et al.* through his study demonstrated that after managing for age and CVD risk factors, ADT use was associated with shorter time to death from CV causes [32].

SPECIFIC DRUG-BASED STUDIES

A prospective study conducted by Smith *et al.* compared leuprolide monotherapy with bicalutamide monotherapy on metabolic changes. Evaluation of subjects was performed at baseline, 3 months, 6 months, 9 months, and 12 months and found that GnRH agonists preferentially increase subcutaneous fat, increase HDL cholesterol and adiponectin levels, and do not change the

waist-to-hip ratio, blood pressure, or C-reactive protein levels [34]. According to The Early Prostate Cancer Trail, bicalutamide showed significant improvement in progression free survival irrespective of primary therapy [35]. Three randomized Phase III trials conducted by Garnick *et al.* compared GnRH antagonist Abarelix to either Goserelin plus Bicalutamide (G+B); Leuprolide (L) monotherapy; or Leuprolide plus Bicalutamide (L+B) in patients with prostate cancer undergoing initial hormonal therapy and included patients with Stage D1/D2 disease, rising prostate specific antigen, intermittent hormonal therapy or neoadjuvant hormonal therapy. It was discovered that hormonal therapy which induces androgen deprivation are all associated with QT interval prolongation [36]. A meta-analysis of an observational study conducted by Garnick *et al.* indicated a favorable link between ADT, notably GnRH agonist (Leuprolide, Goserelin), orchiectomy and the occurrence of CVD events. When compared to males with prostate cancer who were not treated with ADT, GnRH agonists were related to a 38% greater risk of any type of non-fatal CVD [37]. A study conducted by Dockery *et al.* included 43 men with prostate cancer randomly assigned to goserelin or bicalutamide. In a 6-month follow-up they detected an increase in N-terminal pro B-type Natriuretic Peptide which could imply on CV risk following hormonal manipulation [38]. According to a meta-analysis of randomized controlled trials using abiraterone and enzalutamide, abiraterone was linked to an increased risk of CVD, whereas enzalutamide was linked to an increased risk of fatigue [39].

OTHER RISK EVENTS ASSOCIATED WITH ADT

Men who take ADT for prostate cancer suffer from a variety of side effects [40]. Hypertension increases with age [41-44], where approximately 70% of individuals represent 65 years and older. Hypertension is a factor in one out of every seven deaths, and hypertension impacts 70% of people who suffer their first heart attack or stroke [45]. Treatment with new hormonal agents increased the risk of hypertension by 98%. Abiraterone caused 26.2% and 6.9% of all-grade and high-grade hypertension, respectively. There was a significant heterogeneity in all grades hypertension [46]. In an observational study of patients with local or regional prostate cancer in the Veterans Healthcare Administration, it was identified that there exists an association of GnRH agonist and stroke but the mechanism of association was unknown. It was assumed to be the same physiological changes proposed to underlie the risk of CV disease [47]. Induction of hemodynamic and metabolic changes by AST may trigger MI in a predisposed man [48]. A nested case-control study adds to the evidence that ADT may increase the risk of stroke or transient ischemic attack [49]. A total of 239,099 patients from ten trials were included in the meta-analysis. Stroke risk was significantly raised in patients managed with GnRH agonists, orchiectomy, or oral anti-androgens [50]. Although many studies show evidence of CV and cerebrovascular complications following ADT for prostate cancer, few studies have disproved this claim. In a population based observational study consisting of 6,556 men who received GnRH agonist and 3,330 men who underwent orchiectomy as primary treatment, there was no risk of increased CVD among men on GnRH agonist compared to men who had undergone orchiectomy [51]. Several studies have found that CV events occur more frequently within the first 12 months of starting ADT [52]. A meta-analysis of more than 4,000 patients could not gather any evidence that ADT increases CV death among men. On the contrary, they observed a relationship between ADT and enhanced prostate cancer specific survival [53]. Discrepant findings can be accounted for by methodological limitations of observational and randomized studies with respect to association with ADT and CVD [54].

MANAGEMENT

ADT has been shown to improve survival for men with intermediate and high-risk prostate cancer [55-57]. Chemo-hormonal therapies are being studied by many researchers [58-60]. Although certain studies suggest preventive treatments with lipid lowering agents,

Table 1: Hormonal agents used for androgen deprivation in prostate cancer

LHRH agonist	LHRH antagonists	Anti-androgens	Newer anti-androgens (second generation anti-androgens)
Leuprolide	Degarelix	Flutamide	Enzalutamide
Goserelin	Relugolix	Bicalutamide	Apalutamide
Triptorelin	Abiraterone	Nilutamide	Darolutamide
Histrelin			Abiraterone

LHRH: Luteinizing hormone releasing hormone

Table 2: ABCDE steps to reduce CVD in patients with prostate cancer

A	Awareness	Increased awareness among patients about CV signs and symptoms
	Aspirin	Aspirin 81 mg daily for primary or secondary prevention of CV events
B	Blood pressure	Goal blood pressure <140/90 mm Hg
C	Cholesterol	High-intensity statin therapy for pre-existing CVD or hyperlipidaemia
D	Diabetes mellitus	Frequent blood glucose monitoring
	Diet	Metformin for diabetes mellitus if possible Diet rich in fruits, vegetables, and whole grain and low in saturated fat with 600 IU vitamin D daily and adequate calcium (1200 mg/d) Avoidance of excessive alcohol
E	Exercise	150 min/week of moderate-intensity physical activity or 75 min/week of vigorous exercise

Source: American Heart Association, CVD: Cardiovascular disease

anti-hypertensives, OHA, and anti-platelets therapy, if necessary. ADT should not be given to prostate cancer patients who seem to have a history of CV problems [61]. Men with non-metastatic castration-resistant prostate cancer may be capable of minimizing their CV risk by identifying the appropriate therapy (e.g., using newer drugs such as androgen receptor inhibitors) [62]. A study conducted at a community-based practice in the United States discovered that for men with clinically localized prostate cancer and a history of congestive heart failure or MI, treatment with ADT and radiation was associated with a higher all-cause mortality than treatment with radiation alone [63]. AHA recommended steps to reduce CV risk in patients with prostate cancer are elaborated in Table 2 [52].

CONCLUSION

Despite the adverse events, ADT remains as the first line therapy for patients with advanced prostate cancer. Many studies provide a positive relationship between ADT and CV morbidity, although some show no relationship. All patients receiving ADT, including those with pre-existing CV disease, must be evaluated for CV risk factors. As, under-recognition of risk factors and subsequent under treatment may represent an impaired quality of care in survivor populations. Furthermore, there is no evidence providing appropriate and potential treatment options. Some provide prophylactic treatment and, others with supportive management. Further studies should focus both on definite treatment options and on risk factors so to improve care in this population with definite preventive treatment.

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AUTHORS' CONTRIBUTIONS

All authors have contributed equally.

CONFLICTS OF INTERESTS

Author declares no conflicts of interests.

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