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Professional paper

CARDIOVASCULAR DISEASES AND ANDROGEN DEPRIVATION THERAPY

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SUMMARY – The leading cause of death in patients with prostate cancer are cardiovascular diseases. Androgen deprivation therapy is the mainstay of treatment in prostate cancers. The latter has numerous perplexed disadvantaging effects to cardiovascular health. ADT alternates the metabolic profile, insulin resistance and glucose metabolism, causes loss of lean body mass, an increase in adipose tissue, obesity, worsening of atherosclerosis and heart failure. It is important to point out that prostate cancer survivors have increased prevalence of coronary artery disease, cerebrovascular stroke, myocardial infarctions and cardiovascular mortality. Due to these reasons particular care on prevention and treatment of cardiovascular diseases should become a standard of care in patients with prostate cancer.

Key words: *Prostate Cancer; Androgen Deprivation Therapy (ADT); Cardiovascular Diseases; Myocardial Infarction*

Introduction

Cardiovascular diseases are the most common cause of non-cancer related death in patients with prostate carcinoma[1,2]. A number of studies reported on an increased prevalence of major adverse cardiovascular events, particularly myocardial infarction, cerebrovascular stroke and cardiac death in patients treated for prostate carcinoma using androgen deprivation therapy (ADT)[3,4]. Interestingly, in a meta-analysis performed on 4,800 patients there was no difference in thromboembolic risk for patients with therapeutically deprived testosterone, although the cardiovascular mortality was increased in patients with intermittent androgen deprivation[5].

Besides traditional cardiovascular risk factors, especially age or male gender, therapeutic decrease of testosterone levels can have multiple perplexed effects on metabolism, lipoprotein profile and other factors which convene an increase of cardiovascular risk. Through the suppression of gonadotrophin stimulating hormone or blockade of androgen receptors, those lead to decreased stimulation of cancerous cells production by chemical orchidectomy. On the other side, these effects decrease insulin sensitivity, worsen dyslipidemia and increase arterial stiffness[6-8]. Several studies reported on higher prevalence of diabetes and worsening of therapeutic control of diabetes in patients with ADT[9,10]. Preclinical studies on mice revealed more pronounced atherosclerosis in animals with testosterone/androgen receptor deficiency[11]. Analogous findings on increased prevalence of coronary artery disease was also reported in a large retrospective cohort study[12]. In another large population-based observational study, GnRH agonists were associated with higher incidence of peripheral artery disease and venous thrombosis[13]. Furthermore, therapeutic decrease of testosterone levels causes loss of lean body mass, loss of muscle tissue, increase of fat tissue and development of obesity, which is associated with higher cardiovascular risks[14,15]. An-

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drogen deprivation therapy was found to be associated with higher prevalence of arterial hypertension, in a study that analyzed GnRh agonist vs. antagonist during a 3 year follow-up[16].

Negative effects of ADT are furthermore pronounced because of lowered functional performance, i.e. limited lifestyle interventions capacity, increased fatigue and significantly decreased physical activity in patients with prostate cancer and therapeutically decreased testosterone levels[17]. In the propensity score-matched cohort study, the adjusted HR for developing heart failure among androgen deprivation therapy users was 1.92 (95%CI, 1.15-3.18) to propensity score-matched prevalence in nonusers[18]. Data exist on ADT having effect on the prolongation of corrected QT interval (QTc), which might be responsible for higher incidence of sudden cardiac deaths observed in patients with prostate cancer[19]. It is worthwhile to note that in the case of localized prostate cancer, patients' cardiovascular risk has not increased, probably due to a shorter duration of ADT[20].

Epidemiology

A large population-based observational study on 37,443 men who were diagnosed with local or regional prostate cancer and who were treated with ADT in the Veterans Healthcare Administration, reported an increase of cardiovascular comorbidities[9]. Surprisingly, the oral antiandrogen therapy was not correlated with any outcome studied[9]. Arm with GnRH agonists, monotherapy was found to be in correlation with increased risk of incident diabetes (for GnRH agonist therapy, 159.4 events per 1,000 person-years vs 87.5 events for no-androgen deprivation therapy; adjusted hazard ratio [aHR] = 1.28, 95% CI = 1.19 to 1.38), myocardial infarction (12.8 events per 1,000 person-years for GnRH agonist therapy vs 7.3 for no-androgen deprivation therapy, difference = 5.5, 95% CI = 5.4 to 5.6; aHR = 1.28, 95% CI = 1.08 to 1.52), newly diagnosed coronary heart disease (aHR = 1.19, 95% CI = 1.10 to 1.28), sudden cardiac death (aHR = 1.35, 95% CI = 1.18 to 1.54), and cerebrovascular stroke (aHR = 1.22, 95% CI = 1.10 to 1.36)[9]. Complete androgen blockade was associated with a more pronounced risk of incident coronary heart disease (aHR = 1.27, 95% CI = 1.05 to 1.53), whilst only orchiectomy was associated with an increase of coronary heart disease (aHR = 1.40, 95% CI = 1.04 to 1.87), as well as myocardial infarction (aHR = 2.11, 95% CI = 1.27 to 3.50)[9].

The risk of incident coronary artery disease was found to be pronounced within the first four months of treatment[21]. An increase of 20% of serious cardiovascular comorbidity during a 5-year follow-up of patients on ADT was reported[1]. A six-months use of ADT in patients older than 65 years was shown to shorten the period of incident myocardial infarction by 2 years, compared to controls without ADT[3].

One must note that the relation between ADT and cardiovascular diseases and comorbidities might not be defined only as straightforward. GnRH antagonists were found to have protective effects in respect to the increase of cardiovascular risk, whilst other types of ADT's increase the risk of cardiovascular diseases[22]. Other study reported no increase in all-cause mortality with ADT treatment, where the sub-group analysis found no increase of mortality for patients without cardiovascular risk factors or with no known cardiovascular disease, whilst all-cause mortality was higher; adjusted HR 1.96, 95% CI 1.04 to 3.71 in sub-group of patients with myocardial infarction or congestive heart failure due to coronary artery disease[23]. In addition, several studies and meta-analyses also did not report of an increase of cardiovascular diseases in patients with prostate cancer and ADT, making the overall connection somewhat controversial[24-26]. The reasons for discrepancy might be different study settings, the number or selection of patients, various disease and treatment modalities. Further studies are necessary to systematically outweigh the cardiovascular risk associated with ADT[27].

Treatment and prevention

Given the potential of ADT to increase cardiovascular risks, all patients should be advised to reassess their cardiovascular risk profile with their general physician. Science Advisory from the American Heart Association, American Cancer Society, and American Urological Association issued a recommendation that an initial reassessment should be performed within 3-6 months after initiation of ADT, while further follow-up would be tailored individually[28,29]. Basic laboratory exams would be recommended on a yearly basis or otherwise in particular cases[28]. There is a general consensus that prior to the initiation of the ADT no

particular additional routine assessment by cardiologists, internists or endocrinologists should be done[28]. In the circumstance of significant cardiovascular comorbidity, the initiation of ADT should be reassessed by the treating specialist i.e. urologist or oncologist. Currently, there is a lack of evidence-based studies on potential benefits of random or non-incidental, case-based clinical assessment by cardiologists, including stress tests, cardiovascular imaging, coronarography or other diagnostic modalities[30]. It is important to change the lifestyle, correct the diet, increase physical activity and cease with the nicotine abuse[17,33,34].

Conclusion

Androgen deprivation therapy has numerous perplexed negative effects on cardiovascular health. ADT generally has negative effects on commonly known cardiovascular risk factors, especially metabolic ones. Prostate cancer survivors have increased prevalence of significant cardiovascular diseases and major adverse effects as coronary artery disease, myocardial infarctions, cerebrovascular stroke and cardiovascular mortality. Due to these reasons particular care on prevention and treatment of cardiovascular diseases should become a standard of care in patients with prostate cancer

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Sažetak

KARDIOVASKULARNE BOLESTI I ANDROGEN DEPRIVACIJSKA TERAPIJA

M. Boban

Vodeći uzrok smrti u bolesnika s karcinomom prostate su kardiovaskularne bolesti. Terapija deprivacije androgena (ADT) temelj je liječenja raka prostate. Potonja ima brojne nepovoljne učinke na kardiovaskularno zdravlje. ADT pogoršava metabolički profil, inzulinsku rezistenciju i metabolizam glukoze, uzrokuje gubitak mišićne tjelesne mase i povećanje mase masnog tkiva, posreduje u razvoju pretilosti, pogoršava aterosklerozu i dovodi do zatajenja srca. Valja naglasiti u studijama pronađenu dodatno povećanu učestalost bolesti koronarnih arterija, moždanog udara, infarkta miokarda i kardiovaskularnog mortaliteta kod bolesnika s karcinomom prostate i ADT-om. Iz navedenih razloga potrebna je dodatna briga oko prevencije i liječenja kardiovaskularnih bolesti, a navedeno bi trebalo postati standard zdravstvene skrbi.

Ključne riječi: *karcinom prostate; terapija deprivacije androgena; kardiovaskularne bolesti; infarkt miokarda*