Cardiovascular Disease in Men With Prostate Cancer Who Are Receiving Androgen Deprivation Therapy

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In this presentation, Laurence Klotz, MD, FRCSC, of the University of Toronto considers the underlying risk factors for cardiovascular disease (CVD) in men with prostate cancer (PC); discusses the prevention, management, and risk mitigation of CVD in PC; examines the proposed mechanisms of androgen deprivation therapy (ADT)-related CVD; and provides a review of studies evaluating the association between ADT and CVD.

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PC, the most common cancer diagnosed in men, is linked with CVD, Klotz explained.[1,2] Moreover, he said, CVD "is the leading cause of death in all men and also the leading cause of death in men diagnosed with PC, particularly those with localized disease."[1,3,4]

Risk Factors Associated With CVD in Men With PC

Klotz stated that "the risk factors for CVD and PC are remarkably similar."[4] Age is a prominent shared risk factor for PC and CVD, he said. In addition, lifestyle factors, such as smoking and excessive alcohol intake, impact the risk of both diseases.[4] Lifetime diet "undoubtedly influences both the risk for CVD and [death], and the risk for PC," Klotz noted, adding that "a high-fat diet predisposes [patients] to both conditions." Evidence suggests that obesity, visceral adiposity, and lipoprotein levels may have a causal effect on the development of atherosclerotic plaque.[5] He later highlighted that obesity and dyslipidemia both appear to increase the risk of aggressive PC.[4] "There is recent evidence that obesity results in modulation and impairment of immune surveillance in the PC microenvironment [and is] adversely affecting disease progression," Klotz added. As such, obesity also increases the risk of death due to PC.[4]

Another link between these conditions is metabolic syndrome, which is associated with CVD and an increased risk of PC, Klotz stated.[4,6] Notably, metabolic syndrome is also a potential adverse event of ADT.[5-7] Insulin resistance and hyperglycemia are also associated with PC and CVD.[4,8] He emphasized that this is likely the case because high insulin levels tend to be accompanied by high levels of other insulin-like growth factors (IGFs), especially IGF-1, which is known to be a mitogen for PC.[4,8]

Prevention, Management, and Risk Mitigation of CVD in PC

According to Klotz, numerous methods are available to mitigate the impact of CVD associated with ADT; however, he emphasized that these "are not nearly as widely used as they should be." One of the first components of CVD mitigation for patients on ADT is patient and physician awareness of the signs and symptoms of CVD.[9] He underscored the importance of assessing cardiovascular risk before beginning ADT, including an evaluation of the patient for a history of myocardial infarction, stroke, congestive heart failure, peripheral vascular disease, hypertension, chronic obstructive pulmonary disease, and renal impairment.

Klotz also stressed the importance of monitoring patients after beginning ADT. He noted that physicians should monitor blood pressure measurements and blood glucose and lipid levels, especially because "the treatment we are using in these patients alters the lipid profile as well as glucose."[9,10] Appropriate targets for lipids include a low-density lipoprotein (LDL) level less than 100 mg/dL, high-density lipoprotein (HDL) level greater than 40 mg/dL, triglyceride level less than 150 mg/dL, and non-HDL cholesterol level less than 130 mg/dL, Klotz explained. He added that glycated hemoglobin levels should be checked at least once per year, and he recommended referral to an endocrinologist or internist if it rises above 7%.

Lifestyle Modifications

To reduce CVD risk after beginning ADT, Klotz discussed the role of diet and exercise. He mentioned that patients should aim to reduce their intake of animal fat and protein and increase their consumption of fruits and vegetables.[11]

In addition to dietary changes, Klotz underscored the impact of exercise on the mitigation of ADT-associated CVD risk. "Exercise influence[s the] tumor micro-

environment in PC in at least 8 different ways," including epigenetics, cytokine and hormone levels, and immune response, he said. Exercise can also increase muscle mass, reducing the impact of ADT-associated sarcopenia, he added.

Lifestyle changes can also improve the management of CVD in patients on ADT. Klotz stressed the importance of counseling patients on the impact of smoking cessation and avoidance of excessive alcohol.[9]

Medication Management

Following his discussion on lifestyle modifications, Klotz examined the role of medication intervention. He noted that micronutrients and vitamins (eg, vitamin D) may positively impact PC and CVD, but there are no randomized trials to support specific recommendations.

Regarding pharmacologic therapy, Klotz stated that "statins act not just to improve the lipid profile, but they have a direct effect on androgen levels intracellularly." He explained that statins compete for the adrenal androgen dehydroepiandrosterone transporter, which "reduce[s] the substrate available for PC cells to generate their own testosterone and dihydrotestosterone."[12] In a secondary analysis of a study comparing intermittent versus continuous hormonal therapy using the large PR7 cohort of approximately 1500 patients, the addition of a statin was associated with an improvement in the time to androgen-independent progression and PC death.[12]

Considering the role of metformin, Klotz discussed how the drug is typically used in patients with type 2 diabetes.[13] Two small randomized studies of metformin in men treated with ADT demonstrated that compared with placebo, metformin reduced waist circumference and weight gain and lowered insulin and glucose levels."[4] Although numerous population-based studies of patients with diabetes have shown metformin to have a protective effect related to PC progression, metastasis, and mortality,[7] it is not widely used in PC. However, Klotz urged physicians to consider its role "as a preventative agent in men going on ADT."

Proposed Mechanisms of ADT-Related CVD

According to Klotz, treatment for advanced PC has involved ADT for approximately 80 years. However, "the reduction of testosterone to castrate levels induces a version of metabolic syndrome," which consists of 5 key features: increased adipose tissue, insulin resistance, hyperglycemia, dyslipidemia, and hypertension, he said. The clinical attributes of classic metabolic syndrome differ from those of ADT-related metabolic syndrome. He noted that ADT-related metabolic syndrome is frequently associated with subcutaneous fat, whereas classic metabolic syndrome tends to involve visceral fat, which is linked to greater CVD risk. Classic metabolic syndrome is also associated with more serious dyslipidemia: an increased LDL level and decreased HDL level. In contrast, metabolic syndrome induced by ADT tends to involve a significantly increased HDL level, and the LDL level typically remains the same.[2]

In his discussion of follicle-stimulating hormone (FSH), Klotz noted that "there is evidence that FSH is involved in almost every single aspect of the unwanted effects of ADT," including osteoporosis, obesity, and CVD.[14] He specified that the ratio of testosterone to FSH is very important in patients with castrate-level testosterone.

Review of Studies Evaluating the Association Between ADT and CVD

The link between CVD and ADT has remained controversial, owing to disagreement among studies, Klotz explained.[2,15] Observational studies have shown that ADT in patients with PC is associated with an increased risk for CVD.[2] He noted that a systematic review and meta-analysis of observational studies evaluating the potential link between CVD and ADT over the last decade demonstrated a trend toward or a significant relationship between CVD mortality and ADT in all but 1 of the studies examined (HR, 1.17; 95% CI, 1.04-1.32; P=.01).[16]

Randomized controlled trials (RCTs), by contrast, have failed to show a significant link between ADT and CVD, Klotz stated.[2] A systematic review of RCTs found that none were able to demonstrate a significant relationship between CVD mortality and ADT.[17] However, Klotz emphasized that all of these analyses were secondary and not for assessment of a primary end point. He reviewed results published in 2018 from an analysis of numerous different studies and noted that regardless of CVD end point, the effect of ADT was conflicting or inconclusive."[2]

Regarding the differences in results between observational trials and RCTs, Klotz emphasized that there may be limitations in the various study designs, especially selection bias related to the "healthy cohort effect."[2,5] He explained that patients enrolled in clinical trials "tend to be healthier [and] tend to have longer survival than their unselected cohorts in the general population." For example, patients with severe or unstable CVD are typically excluded from participation in oncology clinical trials, he said.[2,5]

Klotz also discussed results from a retrospective study of men with PC from the CaPSURE registry who received local therapy, ADT, local therapy and ADT, or no therapy (watchful waiting/active surveillance [WW/AS]).[15] The patients in the WW/AS subgroup, who were managed conservatively, were likely older and had more comorbidities and risk factors, he said. "It is those factors, rather than treatment-related factors," Klotz reasoned, "that led to the increased rate of CVD mortality."[15]

Conclusions

To conclude his discussion, Klotz stated that "there's a clear link between PC and CVD related to preexisting factors that predispose [patients] to both of these very common diseases." Although there is some uncertainty regarding the relationship between CVD and ADT, numerous interventions may mitigate the unwanted effects of ADT. These include lifestyle modifications, such as diet, exercise, and smoking cessation, and medication-based approaches with statins and metformin. Klotz underscored the importance of a multidisciplinary approach to care involving primary care physicians, cardiologists, and cardio-oncologists to optimize care for patients with PC. ■

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