Prostate cancer is the second leading cause of cancer-related death among men in the United States.[1] Androgen deprivation therapy (ADT) is a common treatment for prostate cancer. ADT includes gonadotropin-releasing hormone (GnRH) agonists (leuprolide, goserelin, triptorelin), bilateral orchiectomy, and anti-androgen receptor blockers such as flutamide and bicalutamide. Several studies have now shown conflicting evidence that anti-androgen therapy may lead to increased cardiovascular morbidity and mortality.[2-5] None of these studies has provided conclusive evidence for causality or a direct link to cardiovascular disease, but they have proposed that therapy side-effects increase parameters that are similar to those of the metabolic syndrome.

Metabolic Effects of ADT

Anti-androgen therapy is associated with several complications, including loss of libido, hot flashes, night sweats, psychological stress, osteoporosis, anemia, fatigue, loss of muscle mass, glucose intolerance, and changes in lipid profile.[6,7] This includes an increase in truncal subcutaneous and muscle adipose deposits, with a decrease in lean body mass but not visceral fat.[8-10] Central obesity is associated with increased cortisol levels, increased plasma-free fatty acids, and insulin resistance. This side-effect is an early adverse effect and is apparent within the first few months of therapy.[11,12] It is accompanied by an increase in serum cholesterol, high density lipoprotein (HDL), and triglycerides.[13,14] These changes in fat deposition, insulin resistance, and lipid profiles are similar, but not identical, to the metabolic dysfunction that contributes to cardiovascular implications.[15] There are clear differences in the hormonal effects of ADT that may counteract or balance their negative impact, such as the increase in HDL and increase in subcutaneous fat rather than visceral fat. Also, inflammatory markers such as CRP, which is elevated in cardiovascular disease, are not elevated in ADT.[11,16] Thus, the side effects of ADT are likely a unique combination with an unclear impact.

Balancing ADT Benefits Against Long-term Side Effects

Eventually, patients who are on ADT attain an incurable androgen-independent state leading to potentially more-severe side effects. Clinicians have to balance the potential therapeutic benefits of androgen deprivation against the long-term side effects, especially the changes in metabolic profile
that this therapy will precipitate. As detection techniques improve, with prostate cancer being diagnosed earlier, the number of patients treated and the length of treatment with ADT will likely increase, making the initiation of ADT even more controversial. Currently it is accepted that patients with metastatic disease receive benefit from ADT, but guidelines are not established for men with isolated disease and for whom benefit is yet to be proven.[18,19] Practitioners will have to be increasingly mindful of side effects as increasing numbers of patients are started on ADT at an earlier date, especially those with established cardiovascular disease and specific high-risk subgroups of patients. In an analysis of the data from the Cancer of the Prostate Strategic Urologic Endeavour (CaPSURE) registry,[5] ADT may increase the risk of cardiovascular death in patients over 65 years of age, and this effect may be related to the length of treatment with ADT. Further detailed research on types of anti-androgen therapies needs to be explored in the future, to assess the risk of heart disease and the extent that these therapies decrease the cardioprotective effects of testosterone. It should also be noted that an equal number of studies can be identified that show no relationship between ADT and cardiovascular risk.[20-22] For example, a European Organisation for Research and Treatment of Cancer (EORTC) randomized trial compared radiotherapy with 6 months of ADT therapy vs radiotherapy with 3 years of ADT in locally advanced prostate cancer, and found no significant difference in the rate of fatal cardiac events at 5-year follow-up.[18]

A recent scientific advisory committee including the American Heart Association, American Cancer Society, and American Urological Association was established as a result of multiple recent studies showing an increase in myocardial infarctions and cardiovascular death among men receiving ADT. This committee agrees that currently there is no evidence that patients for whom ADT is recommended should have cardiac testing prior to initiating therapy or need clearance for therapy from a cardiologist or internist. The decision to start ADT should likely remain between the patient and his oncologist. Patients should be followed closely for the changes in metabolism that may be managed by their internists, however. These patients, especially men with baseline cardiac disease, should likely have aggressive management with lipid-lowering therapy, antihypertensive medications, glucose-lowering therapy, and antiplatelet therapy when appropriate. Healthy lifestyle changes, including smoking cessation, targeting obesity reduction, and increasing exercise, should be advised in these patients.[23]

Financial Disclosure: The authors have no significant financial interest or other relationship with the manufacturers of any products or providers of any service mentioned in this article.

References:

References

Cardiovascular Risk Associated With Androgen Deprivation Therapy
Published on Physicians Practice (http://www.physicianspractice.com)


Source URL:

Links: