“Staging the Aging” When Considering Androgen Deprivation Therapy for Older Men With Prostate Cancer

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It is becoming increasingly clear that androgen deprivation therapy (ADT) is overused in treating prostate cancer. Since Huggins et al.\(^1\) revealed that lowering testosterone levels could slow the growth of prostate cancer, its ability to alter the trajectory of prostate cancer growth has overshadowed the recognition of its impact on other areas of the body. Although athletes have long recognized the role of testosterone in improving muscle strength and overall energy levels, physicians treating older men with prostate cancer have been slower to recognize the converse effect of ablating testosterone on causing accelerated frailty.\(^3\)

ADT was known to adversely impact quality of life (QOL) from the beginning of its use. It has long been known that testosterone-deplete men experience hot flashes, weakness, and fatigue.\(^4\) When ADT was introduced for overt metastatic disease, such QOL impacts were an acceptable trade-off for slowing the growth of cancer and improving life expectancy in men with advanced disease. However, when indications for ADT use were extended from men with metastasis to use for biochemical cancer recurrence (BCR), for adjuvant therapy with external-beam radiation, and for primary therapy for older men, improvements in life expectancy have been uncertain, particularly for lower-grade cancer.\(^5\) Also, newer evidence is suggesting that primary ADT for older men with prostate cancer may actually be lowering disease-specific life expectancy.\(^6\) Thus questions about the adverse impact of ADT on older men are mounting.

Prostate cancer is largely a disease of older men. A majority of patients are older than 65 years, and most of the deaths from prostate cancer are in this age group.\(^7\) As a consequence, any treatments for prostate cancer need to consider their impact in an older population. Prostate cancer is an excellent example of a disease that requires the insight from both oncology and geriatrics. In particular, it is important to consider the impact of treatments on age-associated conditions, such as functional impairments, cognitive impairment, comorbidities, and geriatric syndromes.\(^8\)

The recognized number of comorbidities that ADT adversely impacts continues to accumulate.\(^4,9\) The first to be commonly recognized was bone disease. Smith et al.\(^10\) convincingly demonstrated that ADT led to osteoporosis. As a consequence, it is now standard to order bone densitometry and to place men on bisphosphonates when ADT is initiated if bone mineral loss is present or if it develops on treatment. Newer studies have shown additional effects on so-called geriatric comorbidities, such as functional losses, cognitive impairment, and falls.\(^11\) These consequences have led to the suggestion that ADT can be a significant contributing cause to a new syndrome, known as the androgen deprivation syndrome.\(^12\)

As a result, attention has shifted to understanding the ways ADT affects other prevalent comorbidities of older men. Recently, its potential contribution to cardiovascular disease (CVD), lipid profiles, and diabetes mellitus (DM) has been raised.\(^13\) Given that more older men with prostate cancer will die of CVD than prostate cancer,\(^14\) giving men with (low-grade) prostate cancer a treatment that might exacerbate CVD is concerning. To date, there has been conflicting information regarding the contribution of ADT to CVD and diabetes in older men. An association has been shown for ADT with CVD, fatal myocardial infarction, and DM.\(^13,15,16\) In contrast, analyses of randomized controlled trials have found no dose-response relationship of ADT to CVD or between neoadjuvant ADT and fatal cardiac events.\(^17,18\) Although many of these studies are reasonably large, there are limited numbers of outcome events, and the conclusions are therefore uncertain. Finally, there is mounting data regarding the impact of ADT on metabolic alterations, such as worsening lipid profiles and increased insulin resistance, although nothing directly indicating an association with DM.\(^18,19\) In short, mixed information exists about the role of ADT in worsening CVD or DM. Given the prevalence of these conditions in older men, the group who are most likely to receive ADT, it is crucial that this be understood.

In this context, the article by Alibhai et al.\(^19\) in this issue of Journal of Clinical Oncology contributes vitally important information to this debate. This is the highest-quality data to appear to date on the impact of ADT on the incidence of diabetes. This is an impressive use of a large (n = 19,079) administrative database, with standardized disease definitions, to assess the relationship of ADT to these preidentified outcomes. Along with previously validated algorithms to assess outcomes, the authors use propensity scoring matching techniques to control for age, medication use, income, prior cancer treatments, and other comorbidities. Overall, they do as much as can be done with observational data to assess the association between treatment with ADT for at least 6 months and the outcomes of interest. The most novel finding is the increase in well-characterized incident diabetes in those men undergoing ADT. There was an adjusted hazard ratio of 1.26 (95% CI, 1.16 to 1.36) for the development of new DM, with a number needed to harm due to the use of ADT of 91. This

convincingly supports the conclusion that ADT contributes to the development of DM and that providers should test for underlying hyperglycemia in men being considered for ADT or in men currently receiving ADT who have not been diagnosed with DM.

An equally important, if somewhat paradoxical, finding occurs regarding CVD. The authors report that there is “no relationship” between myocardial infarction and ADT, with an adjusted hazard ratio of 0.92 (95% CI, 0.84 to 1.00). I would consider this result suggestive of an unexpected “protective effect” regarding CVD. Looking at other aspects of their findings among secondary outcomes, the results are even more intriguing. In the analysis of stroke outcomes (Table 1 in Alibhai et al19), treatment with ADT was again “protective” against strokes, with an adjusted hazard ratio of 0.88 (95% CI, 0.81 to 0.88). Finally, in the dose-response analysis, men receiving ADT longer than 24 months were less likely to experience sudden cardiac death than men receiving ADT for a shorter time period, with a hazard ratio of 0.81 (95% CI, 0.69 to 0.96); this is a stronger relationship than the one noted for causing incident diabetes. Collectively, these are surprising findings given the increase in incident DM cases and the known association of that disease with CVD. What explains these two apparently conflicting findings?

The authors offer two hypotheses.19 The first is that there may be a disconnect between new-onset diabetes—a risk factor for CVD—and the eventual development of diagnosed CVD, which can take years. The second is that the other competing comorbidities and associated causes of mortality in this population may be shifted to favor those on ADT. These explanations are only partially compelling, and I would suggest an alternative hypothesis to also consider to account for these findings. In an observational data set, clinicians and patients inevitably select which men will undergo ADT. Such nonrandom selection “sorts” patients on ADT into a lower-risk group for CVD events compared with those not receiving ADT. I suspect that unmeasured covariates correlated with being treated with ADT and with (not) developing CVD are present to a greater degree in those men chosen to be treated with ADT; I further suspect that providers notice these covariates. Such unmeasured covariates cannot be corrected by propensity scoring, which can only control for measured covariates. As has been shown elsewhere, exemplified by the cardiovascular results of the randomized Women’s Health Initiative study, an observational data set cannot avoid such selection effects, and ultimately, a randomized trial is necessary to fully eliminate these effects.20 One candidate unmeasured covariate is number of visits to a provider. Patients undergoing ADT must visit a provider every 3 to 4 months to receive an ADT injection, whereas those not undergoing ADT visit a provider whenever it is deemed appropriate, typically less frequently. As a consequence, perhaps patients undergoing ADT are more likely to have various aspects of their concomitant care addressed. They would be more likely to have their other diseases and CVD risk factors—including diabetes, lipids, and blood pressure—better managed as a result. This would be consistent with another intriguing finding from this article: the strong “protective” effect of having a regular primary care provider preventing sudden cardiac deaths.

Prostate cancer is probably best considered as (at least) two diseases. The first is a life-threatening, high-grade, aggressive cancer that behaves much like other life-threatening cancers. Such cancers, particularly in men with long life expectancies and fewer comorbidities, should be identified early and treated aggressively. The second type of prostate cancer is low-grade, low-volume disease that is more like a chronic disease; such cancers require a less aggressive cancer treatment course and more aggressive management of their overall care. Such low-grade, low-volume cancers, particularly in older men with multiple chronic diseases, functional losses, or cognitive impairments, should be treated considering the context of their cancer occurrence or relapse. ADT has wide-ranging effects on older men, and it should be used as a part of an overall chronic disease management strategy, particularly in the context of low-grade, low-volume prostate cancer. Its use should be integrated into an overall treatment approach that considers remaining life expectancy (not simply age), comorbidities, and functional losses. Approaches such as intermittent ADT, to allow so-called medication vacations, seem to improve QOL without sacrificing life expectancy.21 In short, while we always stage and grade the cancer in choosing cancer therapies, we should also “stage and grade the aging,” to ensure our cancer therapies are integrated into the overall care of our older patients with cancer.22

The cancer specialist’s office may not be the best place for overall consideration of the full range of issues older patients confront in considering the use of ADT.23 In this vein, we point to the finding of Alibhai et al19 of a strong protective effect against sudden cardiac death from having regular access to a primary care physician. Care for older patients with cancer is best accomplished in an environment where cancer specialists work closely with geriatricians and/or other primary care providers to provide truly integrated, comprehensive care.

Author’s Disclosures of Potential Conflicts of Interest

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References


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