Androgen deprivation therapy for prostate cancer: true love or heartbreak?

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The addition of hormonal therapy to radiation therapy improves survival in men with unfavourable risk prostate cancer. Yet, men with prostate cancer have higher rates of non-cancer death than the general population and most will die from causes other than their index malignancy. Comorbid cardiovascular disease is strongly associated with cause of death and this raises the possibility that prostate cancer or its treatment increases cardiovascular disease risk and possibly mortality.

The relationship between androgen deprivation therapy (ADT) and cardiovascular disease is not a new story, although interest has renewed in recent years. Diethylstilbestrol, a non-steroidal oestrogen, was historically used in treating metastatic prostate cancer but was abandoned because of excess cardiovascular and thromboembolic risk. More recently, prospective studies have demonstrated that gonadotropin-releasing-hormone agonists adversely affect some traditional cardiac risk factors, including lipid profiles, insulin sensitivity and obesity. In a large population-based study, Keating et al.[1] reported that these agonists are associated with increased risk of incident diabetes mellitus and cardiovascular disease.

The results of the novel observations by Keating et al.[1] spawned a host of *post-hoc* analyses of randomised trials and observational population-based studies to evaluate the relationship between ADT and cardiac morbidity and mortality.[2–6] To date, the evidence from these studies suggests that ADT modestly increases risk of cardiovascular disease but does not necessarily increase cardiovascular mortality. The absence of an apparent increase in cardiovascular mortality does not, however, exclude the possibility of ADT increasing non-cancer mortality. Previous reports suggested higher non-cancer mortality in men treated with long-term versus short-term adjuvant hormonal therapy for advanced disease[3] and decreased overall survival in those receiving neoadjuvant hormonal therapy before prostate brachytherapy for early-stage disease.[7]

Within this framework, Nanda et al.[8] attempted to evaluate the relationship between short-term ADT and all-cause mortality in men treated with brachytherapy for early-stage prostate cancer. This single-institution, retrospective experience included 5077 men with localised or locally advanced prostate cancer treated

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with or without a median of four months of neoadjuvant ADT followed by brachytherapy. ADT was linked to greater all-cause mortality (P=0.04) after a median follow-up of 5.1 years in a small subgroup (n=256) of men with coronary artery disease- (CAD-) induced congestive heart failure or prior myocardial infarction, but not among the majority of men without those conditions.

We commend the authors on their attempt to define a subgroup of patients in whom ADT is possibly dangerous, and agree that hormonal therapy is not suitable for everyone. Yet, caution must be exercised in the interpretation of the results of this study. First, because prostate cancer is an indolent disease, it is unclear why men with clinically significant cardiovascular disease were treated with brachytherapy rather than managed by active surveillance. Second, there is no established survival benefit for ADT in combination with brachytherapy and it is unclear why so many men received ADT in this setting. Third, there are concerns raised over ascertainment biases in that the main conclusion associating ADT with greater all-cause mortality in men with CAD-induced congestive heart failure or prior myocardial infarction is based on a small subset representing only 5% of the entire study population, and a difference of only seven events.

The choice of all-cause mortality as an endpoint is particularly surprising because the men who received ADT had more adverse features than patients who did not receive it, including older age, and more-aggressive cancers. Unfortunately, the authors did not report cancer-specific or non-cancer mortality, so it remains unclear whether the link to greater all-cause mortality was related to prostate cancer, its treatment, or the selection of patients at greater risk for death.

Notably, an analysis of a large, multicentre, prospective randomised controlled trial with long follow-up found that, even within subgroups of men with high-risk of cardiac death (that is, age 70 years or older, prevalent cardiovascular disease or diabetes) there was no apparent increase in cardiovascular mortality in those treated with adjuvant ADT for locally advanced prostate cancer.[2] Similarly, analyses of another large randomised trial[4] have also reported no excess cardiovascular mortality in men receiving short-term ADT in combination with radiation therapy versus radiation alone.

Herein lies the true lesson of the Nanda study. ADT as an adjunct to radiation was adopted in the 1990s for advanced disease on good evidence. In fact, it is firmly established that hormonal therapy decreases cancer-specific and, in some cases, all-cause mortality for men with locally advanced or high-grade localised prostate cancer. Regrettably, this evidence of improved survival has, in part, led to the increase in the use of hormonal therapy across the entire spectrum of disease even among men with lower-risk prostate cancer and older men with significant competing causes of mortality.[9] This over-exuberant expansion in the indications for hormonal therapy might reflect both the optimism and good intentions of treating physicians; however, the issue of financial reimbursement could be involved as well.[10]

The results of the Radiation Therapy Oncology Group (RTOG) 94-08 study (presented as a late-breaking abstract at ASTRO annual meeting 2009) are of paramount importance to informing proper patterns of practice. This landmark trial demonstrated that short-term ADT before and during radiation therapy modestly improved overall survival (P=0.03) in patients with early-stage localised prostate cancer and notably did not increase the risk of intercurrent death. The actuarial 10-year death rate from intercurrent disease (excluding deaths from prostate cancer) was 35% in the ADT plus radiation therapy arm and 37% in the radiation alone arm (P=0.49). The results of the risk group analysis revealed that the intermediate-risk subgroup experienced the greatest benefit from short-term ADT, although it is debatable whether this remains valid in the era of dose-escalated radiation therapy (which is being addressed in an ongoing RTOG trial). Results of this risk group analysis, however, demonstrate that there is no role for hormone therapy in low-risk disease. Secondary analyses from this important randomised trial will help shed further light on the unintended adverse effects of hormonal therapy in early-stage disease, including those with significant cardiac comorbidity.

We strongly recommend limiting use of adjunctive ADT to settings with an established survival benefit. These evidence-based indications include men receiving external-beam radiation therapy for intermediate and high-risk disease. The absence of an established survival benefit should be sufficient reason to avoid ADT in other settings, including men receiving brachytherapy and/or external-beam radiation therapy for low-risk disease. The increased understanding of potential adverse effects of ADT serves to reinforce careful selection of appropriate candidates for treatment.

Clinicians should not necessarily withhold ADT from men who might benefit from it in terms of cancer-specific survival despite a history of cardiac comorbidity after careful consideration of the risks and benefits. Good general medical care dictates that patients with underlying cardiac disease receive secondary preventive measures, including lipid-lowering, antihypertensive, glucose lowering, and antiplatelet therapy as appropriate. There is no evidence to recommend additional cardiac testing or coronary intervention in patients with cardiovascular disease before initiation of ADT. In lieu of a randomised controlled trial directly

addressing the question of the effect of ADT on cardiac health, we believe future trials of ADT as well as novel forms of hormone therapy should prospectively assess cardiovascular risk factors and stratify patients according to their comorbidities.

The questions raised by the relationship between ADT and cardiac health in prostate cancer patients are complicated. The initial excitement surrounding hormonal therapy could now be over, as the relationship finds a new balance based on evidence.

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Practice point

Androgen deprivation therapy is associated with many adverse effects, including cardiovascular disease. Its use as an adjunct to local therapy, such as radiation, in the treatment of prostate cancer should be limited to settings with proven survival benefit.

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