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EDITORIAL COMMENT

Duration of Androgen Deprivation Therapy and Cardiovascular Fitness

Delivering the Right Patient the Right Therapy at the Right Time*

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Androgen deprivation therapy (ADT) remains the fundamental systemic anticancer therapy for men with advanced prostate cancer. Since the early 1980s, ADT has been achieved most commonly with the use of gonadotropin-releasing hormone (GnRH) agonists, which induce marked suppression of gonadal testosterone production. Such medical castration results in robust therapeutic responses in most men with advanced prostate cancers, owing to the exquisite sensitivity of prostate cancer to oncogenic androgen signaling. Indeed, in contemporary clinical management, ADT is often coupled with potent secondary agents to further attenuate androgen signaling and enhance anticancer efficacy (1,2). However, this prolonged and intensive androgen suppression is known to induce numerous consequences for male metabolic health, including dyslipidemia, loss of bone mineral density, and sarcopenic obesity (3,4). Moreover, for the past decade, standard GnRH agonist therapies have carried an advisory from the Food and Drug Administration warning of increased treatment-related cardiovascular risks, including myocardial infarction, stroke, and sudden cardiac death (5). Thus, although ADT confers significant prostate cancer therapeutic efficacy, these observed competing health risks carry profound clinical importance, especially for a typical prostate cancer patient population composed of elderly men with coexisting medical morbidities. As a result, an improved understanding of the patient- and treatment-related factors associated with ADT-related cardiovascular risk is necessary to appropriately counsel patients with prostate cancer and to mitigate cardiac risks.

In this issue of *JACC: CardioOncology*, Gong et al. (6) evaluate the association between ADT exposure and cardiorespiratory fitness and CV mortality in patients with prostate cancer previously treated with curative intent. In particular, the investigators sought to evaluate the effects of prolonged ADT duration (>6 months) on these clinical outcomes. The authors' key finding of an observed increased risk of reduced cardiorespiratory fitness following prior ADT exposure, largely driven by those patients receiving prolonged ADT treatment durations, is notable and complements the existing clinical knowledge base. Many of the adverse metabolic effects of ADT, including weight redistribution, loss of lean muscle mass, and loss of bone mineral density, may be cumulative in nature, and as a result, prolonged ADT durations may affect cardiorespiratory fitness and other functional outcomes to a greater degree (4). Further, increasing age in a predominantly elderly population is an independent risk factor for cardiovascular disease that also appears to synergistically increase cardiovascular risk associated with prolonged durations of ADT (7). The known prognostic significance of reduced cardiorespiratory fitness, coupled with the other well-described metabolic changes that occur during ADT

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exposure, support the authors' findings of a strong association between ADT duration and increased cardiovascular mortality.

However, some caution should be observed in the interpretation of these results. In particular, the absence of a significant association between shorter durations of ADT exposure and adverse cardiorespiratory fitness in this patient sample does not exclude this possibility. In fact, prior studies evaluating the risk and timing of CV events in men treated with ADT indicate that the CV risk may be greatest within the first 6 months of ADT exposure (8). Furthermore, several of the proposed mediators of the negative association between prolonged ADT exposure and adverse cardiovascular fitness, including increased lipids, insulin resistance, and increased body mass index, have been shown to largely occur within the first 6 months of ADT exposure (9). Thus, shorter durations of ADT exposure may still carry adverse cardiometabolic risks, especially in those with baseline cardiovascular risk factors. Indeed, in a hypothesis-generating analysis of a randomized clinical trial, a "short duration" of 6 months' ADT exposure was associated with significantly decreased overall and cardiac mortality among patients with prostate cancer with underlying medical comorbidity, when compared with no ADT exposure (10). Ultimately, a prospective clinical study with a primary endpoint of cardiovascular events and assessments of changes in cardiovascular fitness, lipids, insulin resistance, and other cardiovascular risk factors may be the only way to definitively describe the relationship between ADT duration and cardiovascular events and clarify the underlying biologic mechanisms.

Nevertheless, given the central reliance of prostate cancer on androgen signaling, ADT will remain a fundamental and critical prostate cancer treatment modality. Indeed, the earlier use of intensified androgen suppression regimens for longer treatment durations is increasingly used in clinical practice, based on demonstrated improvement in survival outcomes for many patients with advanced prostate cancer (11). However, this clear oncologic benefit with improving survival outcomes further highlights the need for increased attention to potential cumulative treatment-related toxicities, competing health risks, and health-related quality-of-life in this population (12). One population-based retrospective evaluation of patients receiving intensified combination androgen suppression with a GnRH agonist plus the potent androgen signaling inhibitors, abiraterone acetate or enzalutamide, demonstrated increased all-cause mortality in men with underlying cardiovascular comorbidities (13). Further attention to the cardiovascular complications of these increasingly common combination treatment approaches is critical as oncologic treatment strategies evolve.

Moving forward, improving cardiovascular and metabolic outcomes in patients with prostate cancer will likely require: 1) use of ADT strictly for appropriate evidence-based indications and treatment durations; 2) improved attention to cardiovascular risk factor mitigation in this population; and 3) testing of novel therapies and cardiovascular risk-mitigation strategies. Although consensus guidelines informing the appropriate use of ADT have been published by oncologic and urologic organizations, the optimal use, timing, and duration of ADT remains highly variable in routine prostate cancer clinical practice (14). As highlighted by the accompanying publication, some cardiometabolic toxicities of ADT may be cumulative and dependent on the duration of therapy, therefore emphasizing the importance of adherence to evidence-based ADT treatment durations. In addition, recent evidence indicates that cardiovascular risk factors are commonly underrecognized and undertreated in patients with prostate cancer planned for ADT initiation (15,16). Improvement in both medical and lifestyle cardiovascular risk factors in patients receiving ADT through standardized practical clinical algorithms like the "ABCDE approach," will require enhanced collaborative efforts between prostate cancer providers, cardiologists, and general internists, and may yield improved outcomes for patients (17). Finally, novel therapies with improved cardiac toxicity profiles are needed. Notably, recent findings from a large phase 3 randomized trial of the novel oral GnRH antagonist relugolix versus the GnRH agonist leuprolide demonstrated a lower incidence of major adverse cardiovascular events with relugolix, particularly in those patients with underlying cardiovascular disease history (18). Further research should seek to validate this finding and to investigate underlying mechanisms for this improved cardiac safety. In terms of strategies to improve modifiable, lifestyle factors, an ongoing international phase 3 randomized trial is evaluating the use of supervised high-intensity aerobic and resistance training in patients with advanced prostate cancer receiving ADT (NCT02730338) (19). Although the primary endpoint of this trial is overall survival, key secondary endpoints will evaluate validated physical quality-of-life metrics and

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physical functioning (such as cardiopulmonary exercise and 400-m walk tests).

By improving our understanding of the patient- and treatment-related factors contributing to ADT-related cardiac toxicity, oncology and cardiology providers can work collaboratively to optimally use such therapy modifications and cardiovascular risk-mitigation strategies. Ultimately, success will come when we simultaneously maximize both cardiovascular and cancer outcomes for each man, ensuring that we have the right patient receiving the right therapy at the right time.

AUTHOR DISCLOSURES

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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