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Editorial

EDITORIAL

Cardiovascular and Metabolic Diagnoses Associated With Novel Hormonal Agents for Prostate Cancer in Nontrial Populations

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Androgen deprivation therapy with gonadotropin-releasing hormone (GnRH) therapy or orchiectomy has been used for many years to treat advanced-stage prostate cancer. Such treatment is highly effective for arresting tumor growth but has numerous adverse effects, including fatigue, loss of muscle mass, vasomotor instability, bone loss, and metabolic abnormalities. Androgen deprivation therapy is also associated with an elevated risk for cardiovascular disease and diabetes (1-3). In the past decade, 2 novel hormonal agents, abiraterone and enzalutamide, have greatly expanded treatment options for prostate cancer. Less is known about their adverse effects, particularly for population-based cohorts of individuals who may not be well represented by clinical trial participants.

In this issue of the Journal, Lai et al (4) examine the risk of metabolic and cardiovascular adverse events among patients with advanced prostate cancer being treated with abiraterone or enzalutamide. Although clinical trials have demonstrated favorable toxicity profiles for these treatments, the individuals who enroll in cancer clinical trials are typically younger and healthier than the general population of individuals with cancer, and thus, findings from trials may not generalize to all individuals with prostate cancer. Moreover, clinical trials often have limited follow-up, and they may be underpowered to detect relatively small but clinically important adverse effects.

Using data from a 20% random sample of fee-for-service Medicare beneficiaries, the authors identified a large population of patients with presumed advanced prostate cancer based on chronic androgen deprivation therapy use, defined as bilateral orchiectomy or at least 6 months of continuous GnRH therapy (4). They excluded patients with recent radiation therapy for whom the GnRH treatment may have reflected adjuvant androgen deprivation therapy for patients without advanced disease. The authors then examined rates of major metabolic and cardiovascular adverse events for patients treated with abiraterone or enzalutamide in addition to androgen deprivation therapy vs androgen deprivation therapy alone. The primary outcome of major metabolic or cardiovascular events was defined as an emergency department visit or hospitalization with a primary diagnosis of diabetes, hypertension, congestive heart failure, coronary artery disease, or dysrhythmia. Of note, to better identify new events, the authors excluded individuals with an emergency department visit or hospitalization with a primary diagnosis for 1 of these conditions in the prior 12 months; this is likely to bias towards the null, assuming patients with existing cardiovascular disease would be more likely to experience events. The authors also assessed minor metabolic or cardiovascular events, focusing on outpatient visits with the same diagnosis codes as for the primary outcome assessing major events, again excluding individuals with the relevant outcome in the prior 12 months.

Both abiraterone and enzalutamide were associated with the primary outcome of major metabolic or cardiovascular events, although the hazard ratios (HRs) and confidence intervals (CIs) were higher for patients receiving abiraterone (HR = 1.77, 95% CI = 1.53 to 2.05) than for patients receiving enzalutamide (HR = 1.22, 95% CI = 1.01 to 1.48) (4). Patients treated with abiraterone had an unadjusted 9.4 major events per 100 person-years during treatment (a median of 4.7 months) compared with 5.9 per 100 person-years for those not on abiraterone, reflecting 1 additional major cardiovascular event for each 29 patients treated. In analyses of minor cardiovascular events assessed based on outpatient visits, abiraterone was associated with new diagnosis of diabetes, consistent with findings of other studies examining other forms of androgen deprivation therapy (1,3). Interestingly, enzalutamide was associated with a lower risk of diabetes in the analysis of minor events.

The differences observed between abiraterone and enzalutamide may be related to their mechanisms of action. Abiraterone prevents testosterone synthesis by inhibiting the cytochrome P450 17A; it also decreases glucocorticoid production, with a related increase in adrenocorticotrophic hormone and mineralocorticoid excess that can cause hypertension, hypokalemia, and fluid retention. To limit these adverse effects, it is given with oral prednisone, which can cause fluid retention and insulin resistance. Enzalutamide is an androgen receptor blocker that also

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increases glucocorticoid levels. A previous meta-analysis of clinical trials of abiraterone and enzalutamide found an increased risk for all-grade cardiovascular toxicity for both drugs, with abiraterone increasing risk of both cardiac events and hypertension events and enzalutamide only increasing risk of hypertension events (5). A comparative effectiveness study using Canadian health-care data similarly found a higher risk of cardiovascular-related hospitalizations for individuals treated with abiraterone vs enzalultamide (6). The coadministration of prednisone with abiraterone may explain the higher risk of diabetes events.

A challenge of this type of observational research is the inability to demonstrate causal relationships. The study by Lai et al. (4) was conducted with rigor, and the findings were robust in a series of sensitivity analyses. A falsification test assessing the outcomes associated with a medication or procedure not likely to affect the outcomes, such as proton pump inhibitor therapy or a knee x-ray, may have provided additional evidence to support a causal relationship. Nevertheless, the findings add to growing evidence of the importance of considering cardiovascular and metabolic effects of prostate cancer treatments and thus have important clinical implications.

As the indications for these novel hormonal agents continue to expand to include patients with both locally advanced and metastatic prostate cancer and as duration of use increases, the potential impact on cardiovascular and metabolic health is important to consider. Cardiovascular disease is the most frequent cause of noncancer death among individuals with metastatic prostate cancer (7). Although more research is needed to fully understand the mechanisms for cardiovascular disease risks and differences between enzalutamide and abiraterone, the existing evidence suggests that there is likely some increase in risk of cardiovascular disease with these treatments as well as elevated blood sugars and diabetes risk with abiraterone. Decisions about initiating abiraterone or enzalutamide should include discussions with patients about both benefits and harms of the treatments, including the potential cardiovascular and metabolic adverse events, and consider existing comorbidities in treatment choice. In addition, regardless of the treatment selected, urologists and oncologists should engage patients' primary care clinicians and together support behavioral changes that can lower risks for diabetes and cardiovascular disease, including prioritizing healthy diet and regular exercise. Clinicians should also discuss other strategies for cardiovascular and diabetes risk reduction based on patients' risk profiles (8-10). Looking beyond the tumor to consider the whole patient will help to optimize the overall health of individuals being treated for prostate cancer.

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