Editorial

Androgen Deprivation for Prostate Cancer

The Case for "First, Do No Harm"

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The beneficial effects of androgen deprivation on prostate cancer have been known for more than a half century, based on work demonstrating the androgen dependency of prostate tumor cells.[1] Androgen deprivation therapy (ADT), initially in the form of bilateral orchiectomy, has accordingly long been a mainstay for the palliation of metastatic prostate cancer. For most of its history, concerns about side effects of the therapy have mainly related to sexual dysfunction and constitutional symptoms. Much more recently, there has been a paradigm shift to an appreciation that ADT may have more serious, life-threatening consequences. These include fractures, cardiovascular disease, diabetes mellitus, and even colorectal cancer.[2-4]

Increasing recognition of these adverse effects has occurred for several reasons. There has been a substantial change in ADT use over the last 15 years. Use of ADT doubled over the course of the 1990s, mainly in the form of gonadotropin-releasing hormone (GnRH) agonists (an injectable form of medical androgen deprivation), which are far more palatable for patients than orchiectomy, coupled with an overall broadening of the indications for ADT.[5,6] Instead of being limited to just palliation, ADT started being used as an adjuvant treatment with radiation and surgery in some settings, as well as a primary treatment even in nonmetastatic cases. Particularly when used as primary treatment for localized tumors, the period of exposure is potentially long, even decades. The net result was that many more men were exposed to ADT (a prevalence of more than 500,000 men by 2000 in the United States alone), and for much longer durations, thus increasing the likelihood of side effects.[7] In addition, the availability of databases that included large cohorts of men with prostate cancer enabled the detection of these effects. The Surveillance, Epidemiology and End Results (SEER)-Medicare database, which has been particularly useful for this purpose,[8] consists of a collection of data from mostly state-based cancer registries, linked to Medicare claims of the patients. Many of the relative risks of side effects associated with ADT have been relatively modest, requiring large sample sizes in order to detect them with precision. These risks may nevertheless be important given high underlying rates of some of the adverse outcomes in elderly men, such as fracture and cardiovascular disease.

In this issue of *Cancer*, Ehdaie et al.[9] add yet another potential consequence of ADT use, with a SEER-Medicare based analysis demonstrating an increased risk of thromboembolic events (TEs). After applying standard exclusions such as those patients enrolled in managed care plans, the resulting analytic cohort consisted of 154,611 men with incident prostate cancers diagnosed from 1999 through 2005. The median study follow-up available was 52 months. The primary outcome was a TE, defined as a deep venous thrombosis, pulmonary embolism, or arterial embolism, based on the presence of the relevant *International Classification of Diseases*, 9th Revision (ICD-9) diagnosis codes in the claims data. The exposure of interest was ADT, defined either by bilateral orchiectomy or use of GnRH agonists. The main modeling approach was a Cox proportional hazards regression, with ADT entered as a time-dependent variable along with other covariates such as demographics, tumor characteristics, other cancer treatments, and comorbidity. Of the study cohort, 38% received ADT. The primary outcome developed in 15% of men in the ADT group versus 7% in the group who did not receive ADT. About half of the TEs were deep venous thromboses, and a quarter overall were associated with a hospitalization. In the Cox model, the adjusted relative risk of a TE associated with ADT was 1.54 (95% confidence interval,

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1.48-1.89). Because the underlying biological mechanisms may be distinct, the authors also examined the risk of arterial and venous TEs separately, and found an increased risk associated with ADT for both outcomes.

To assess the credibility and importance of these findings, several issues must be considered. Selection bias is a major concern in this context. Patients who receive ADT tend to be older and have more comorbidities, because they are often not candidates for more "aggressive" treatment options involving radiation or surgery.[8] ADT is also more often used with advanced stage cancers and those with tumor characteristics associated with a high likelihood of progression or recurrence. These patient and tumor characteristics may plausibly be associated independently with an increased risk of TEs, and could therefore confound the relationship between ADT and TEs. To address these issues, the authors used a standard multivariable Cox regression approach to adjust for available confounders, and in addition, provided results stratified by age and tumor characteristics. The association between ADT and TEs was maintained after adjustment, and results were consistent across strata, including among patients with low-risk tumors (tumor stage of T2 or less and Gleason score ≤ 6), who would be unlikely to develop progressive or recurrent disease over the course of study follow-up.

Some important risk factors for TEs, such as smoking and baseline obesity were not available in the dataset, but because these are not plausibly associated with use of ADT, they would not be confounders in the analysis. The possibility of unmeasured and/or unknown confounders always remains a concern with any observational study, however. Ascertainment bias is another potential concern. This can occur due to the more frequent medical contacts among men receiving GnRH agonists, which may lead to the detection of events that may have otherwise been clinically silent. Other SEER-Medicare–based analyses have addressed this either by examining the association with outcomes resulting in a hospitalization (which would be less susceptible to ascertainment bias) or by directly adjusting for frequency of medical visits in the model.[2,4] Neither of these approaches were used by the authors, but they did examine separately the effect of orchiectomy and GnRH agonists on the outcome, which can be illuminating. If the observed association is truly due to androgen deprivation, it would be expected that the risk would be greatest with orchiectomy, because it produces a permanent and complete castration. However, because men with orchiectomy do not receive as intense medical

follow-up as those receiving GnRH agonists, the risk observed with orchiectomy may be lower if ascertainment issues are indeed present.[4] The latter pattern was seen, for example, in a study that examined cardiovascular risks of ADT, an area for which the data continues to be conflicting.[3] In contrast, in the study by Edhaie et al., orchiectomy was clearly associated with a higher risk of TEs than was GnRH agonist use.

It is also important to assess features that help establish that the observed association may indeed be causal. One criterion is consistency, based on the presence of other studies using different cohorts of patients that corroborate the findings. A Swedish study published last year examined the risk of TEs in a large cohort of men with prostate cancer in comparison with the general population. As expected, the risk of TEs was elevated overall in men with prostate cancer compared with the general population, but the risk was even higher in the group who received ADT.[10] Interestingly, the increased risk was demonstrable for venous but not arterial TEs, in contrast with the study by Ehdaie et al. A second criterion is biological plausibility. Available evidence in this regard is quite limited, although there are potential mechanisms by which ADT could contribute to the risk of TEs. ADT is well-documented to lead to obesity, which is itself an independent risk factor for venous TEs.[11,12] Although androgens appear to have an inhibitory effect on arterial thrombosis in some studies,[13,14] this finding is not consistent with or is even contradicted by other studies.[15] A third criterion is the demonstration of a gradient in the effect. This is typically assessed as a dose response, but in the context of studies of ADT, it has usually been examined as a duration response effect. The authors examined the effect of duration of ADT on the risk of TE, showing steadily increasing risk as the duration of ADT was increased from <1 year to 1 to <3 years to ≥ 3 years.

A final point is the need to assess potential clinical importance of the study finding, assuming a true effect. This is best accomplished by examination of differences in the *absolute* risks of the outcomes as a function of ADT exposure, which would allow estimation of the number needed to harm (ie, the number of men treated with ADT that would lead to an additional adverse event). Unfortunately, the authors do not present measures of absolute risk differences or incidence of TEs that allow calculation of those risks. Only frequency information is presented, which at least suggests that TEs are fairly common in the setting of prostate cancer. A quarter of the events were associated with a hospitalization, suggesting a substantial

clinical impact in many cases. Overall, the available data provide fairly compelling evidence that ADT contributes to the risk of TE; major caveats are the possibility of unmeasured confounding, as well as the relatively weak evidence base supporting biological plausibility.

How should the potential risk of TEs due to ADT affect management of men with prostate cancer? As the authors suggest, for men already on ADT, physicians and patients need to perhaps be more vigilant for TEs, but this is unlikely to be a major departure from current management, because all patients with prostate cancer are already at increased risk for TEs. Mitigating or preventing the consequences of ADT remains a major challenge, even for the most-studied effects, such as osteoporosis and fractures. In the latter case, despite extensive research and multiple available treatments, definitive evidence of efficacy for fracture reduction is still lacking.[16] Furthermore, bisphosphonates, one of the most commonly used agents to prevent osteoporosis and fractures, have themselves now been shown to have potentially serious side effects.[17] The best strategy to minimize the impact of complications from ADT is therefore to restrict its use to settings where its benefits clearly outweigh negative consequences. Use of ADT in symptomatic metastatic disease is one such example, because palliation is the overriding concern, and life expectancy is likely to be quite limited. In addition, ADT can be used in settings in which high-quality clinical trial evidence of overall survival benefit exists, such as adjuvant therapy with radiation for locally advanced or high-risk tumors.[18] Even in the latter scenario, some caution is warranted in light of evidence that some men with preexisting comorbidties may not benefit from ADT.[19] In settings where benefits are uncertain, such as primary treatment of asymptomatic disease or biochemical recurrence, ADT should ideally not be used at all. If patients or physicians feel compelled to use ADT in these settings, this should only occur after a thorough discussion of the potential harms and uncertain efficacy.

Given the available evidence to date, the story of ADT for treatment of prostate cancer should be viewed as a cautionary tale. Originally developed successfully for the palliation of metastatic disease, its use expanded dramatically since the 1990s, often in settings where its benefits were far from clear. This was undoubtedly driven in part by a desire by both physicians and patients to "do something" in the face of a cancer diagnosis. Some physicians likely even felt pressured to use ADT, as evidenced by surveys showing many physicians who prescribed it did not even believe in its efficacy.[20] Disturbingly, there is now convincing evidence that financial influences also played a part in the growth of ADT. Use of GnRH agonists allowed for substantial profits, and private practice urologists were significantly more likely to prescribe them in settings of uncertain benefit than academic urologists.[21] More recently, drastic cuts in reimbursement for GnRH agonists led to dramatic reductions in use of ADT.[22]

Since 2005, the list of serious consequences of ADT has been growing, with the article by Ehdaie et al. adding to it. Ultimately, it seems likely that tens of thousands of men with prostate cancer have been needlessly harmed by the use of ADT. The specter of financial gain for use of ADT only compounds that tragedy. The moral of the story is clear: When faced with clinical decisions in the setting of uncertainty, physicians must never forget their responsibility to "first, do no harm."

CONFLICT OF INTEREST DISCLOSURE
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