PROSTATE CANCER

ADT—who, when and for how long?

Decreasing the duration of androgen deprivation therapy (ADT) in men receiving radiotherapy for locally advanced prostate cancer compromises their survival.

Interim analysis of data from a European trial in which 970 men were randomized to 3-dimensional conformal radiotherapy (70 Gy) plus either short-term or long-term treatment with a luteinizing hormone-releasing hormone agonist has shown that cessation of ADT after 6 months—compared with 3 years—is associated with an increased risk of death (hazard ratio 1.42).

After a median follow-up period of 6.4 years, 132 men in the short-term group and 98 in the long-term group had died; 47 and 28, respectively, from prostate cancer. There was no marked difference in overall quality of life between the two groups. On the basis of these findings, the investigators recommend that 3 years remain the standard duration of ADT accompanying radiotherapy for locally advanced prostate cancer. Commenting in *JournalWATCH*, Robert Dreicer (Chair of Solid Tumor Oncology at the Cleveland Clinic) cautions that these "results do not address the management of low-risk or intermediate-risk patients, nor can they be extrapolated to patients who are managed with brachytherapy."

A notable secondary outcome of the European trial was the lack of difference in 5-year cumulative incidence of fatal cardiac events between the short-term and long-term ADT groups. There has been increasing concern about the potential cardiovascular effects of androgen ablation, but conflicting data abound. Now, publication of the results of a population-based study indicate that continuous ADT lasting 6 months or more does not increase the likelihood of recipients suffering acute myocardial infarction or sudden cardiac death. By contrast, the risk of developing diabetes is elevated by ADT.

The Canada-based research team used linked databases to match prostate

cancer patients aged at least 66 years who had received ADT (as either bilateral orchiectomy or medical androgen suppression) with an equal number of men who had not received these treatments. Data from just over 19,000 matched pairs were analyzed.

Adjusted hazard ratios for new myocardial infarction and sudden cardiac death were 0.92 and 0.96, respectively. Conversely, men who had received ADT were 25% more likely to become diabetic. Diabetes is a well-recognized risk factor for cardiovascular disease. As such, it is reasonable to expect that an increase in the incidence of diabetes would be associated with a greater number of cardiac events. How might this apparent discrepancy be explained?

The authors of the database analysis, published in the *Journal of Clinical Oncology*, postulate that the temporal lag between onset of diabetes and its effect on cardiovascular risk underlies the observation. In an accompanying Editorial, William Dale (Geriatrics, Palliative Medicine, and Hematology/Oncology, University of Chicago) suggests that the nonrandom allocation of patients in observational studies such as this also influenced the outcomes. That is, healthier patients with fewer cardiovascular risk factors were more likely to have been prescribed ADT.

Dale and colleagues have recently shown that another patient-related factor—anxiety—strongly influences treatment decisions. High levels of disease-specific anxiety among older men independently predicted early commencement of ADT following biochemical recurrence (odds ratio 9.19). As the optimal timing for initiation of hormone therapy is far from precisely defined, are clinicians doing enough to counsel their patients about the tradeoffs between potential benefits and adverse effects?

"It is becoming increasingly clear that ADT is overused", states Dale in his Editorial. "There is a propensity to 'do something' about cancer that leads to starting a therapy that is not justified" he told *Medscape Oncology*. Peter Albertsen from the University of Connecticut Health Center, who commented in *The New England Journal of Medicine* on the European trial conducted by Bolla *et al.*, agrees. Also speaking to *Medscape Oncology*, he explained that the overuse of ADT has probably been at least partly driven by clinicians overestimating its effectiveness.

In general, the available data indicate that early initiation of ADT should be limited to men with metastatic disease and those younger than 65 years receiving radiotherapy for high-risk prostate cancer. Dale also suggests that testing for hyperglycemia be incorporated into the pre-ADT workup.

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Original articles Bolla, M. *et al.* Duration of androgen suppression in the treatment of prostate cancer. *N. Engl. J. Med.* **360**, 2516–2527 (2009).
Alibhai, S. M. H. *et al.* Impact of androgen deprivation therapy on cardiovascular disease and diabetes. *J. Clin. Oncol.* doi:10.1200/JCO.2008.20.0923
Dale, W. *et al.* Patient anxiety about prostate cancer independently predicts early initiation of androgen deprivation therapy for biochemical cancer recurrence in older men: a prospective cohort study. *J. Clin. Oncol.* **27**, 1557–1563 (2009).