PROSTATE CANCER

Dutasteride—a welcome addition to active surveillance?

Progression of low-risk prostate cancer can be delayed with daily dutasteride, according to results of the REDEEM (Reduction by Dutasteride of Clinical Progression Events in Expectant Management) trial, recently published online in the *Lancet*. Experts hope that this promising finding might lead to increased uptake of active surveillance by suitable men.

Dutasteride is a 5 α reductase inhibitor, which blocks the production of dihydrotestosterone from testosterone, and causes a reduction in prostate volume and PSA. It is currently approved for the treatment of benign prostatic hyperplasia, but last year the FDA rejected an application for its use in prostate cancer prevention owing to controversy regarding data from the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) study. REDUCE was performed in patients who did not have prostate cancer but were at high-risk of developing it. Although a reduced incidence of prostate cancer was indeed demonstrated in men who received dutasteride, treated patients were also shown to be at increased risk of developing high-grade (Gleason 8–10) disease (RR 2.06; 95% CI 1.13–3.75).

Neil Fleshner and colleagues in Toronto, Canada, initiated the REDEEM trial to address whether dutasteride could slow the progression of low-risk prostate cancer and, therefore, reduce the need for intervention. 302 men on active surveillance, aged 48–82 years, with stage T1c–T2a prostate cancer and a Gleason score of ≤ 6 were recruited from centers across Canada and the USA. They were randomized to receive either 0.5 mg dutasteride or placebo every day for 3 years.

The primary end point of REDEEM was time to progression, which was categorized as either pathological progression (involvement of ≥ 4 cores on 12-core biopsy or involvement of $\geq 50\%$ of any one core or Gleason pattern ≥ 4) or therapeutic progression, meaning the point at which the patient underwent definitive treatment.

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At 3 years, progression was reported in 38% of men who received dutasteride and 48% of the control group, which translates to a 38% decreased risk of progression for patients in the treatment group (HR 0.62; 95% CI 0.43–0.89; $P = 0.009$). Incidence of high-grade disease did not differ between groups (14% in the dutasteride arm versus 16% in controls), and similar rates of drug-related adverse events were reported in each arm. In particular, cardiovascular effects were reported by 5% of patients in both groups ($P = 0.79$).

Active surveillance is gaining popularity as a management option for men whose prostate cancer is not life-threatening. Unfortunately, uptake remains limited in the USA, probably because anxiety related to inaction can push patients towards active treatment, regardless of the attendant risks of incontinence and impotence. “Systemic drug therapy, as studied in REDEEM, offers these patients another option with biologic and psychologic advantages over doing nothing at all,” says Larry Goldenberg, a prostate cancer specialist who was not involved in the study. “The demonstrated 38% delay in progression at 3 years without evidence of upgrading to higher-risk cancer is highly relevant in the clinical realm, as it will undoubtedly ease the

anxiety that many of these men and their partners experience.”

Other clinicians do not support the use of dutasteride in active surveillance. In an accompanying editorial comment, Chris Parker from the Royal Marsden NHS Foundation Trust in the UK, explains his reservations. Parker believes that time to therapeutic progression is a flawed end point given that the investigators knew which patients were taking dutasteride based on their lower PSA levels, and this might have affected the decision to instigate treatment. Furthermore, he highlights that the rate of pathological progression alone was not significantly better in the dutasteride group (29% versus 33% in placebo arm).

Whether dutasteride, or other chemopreventative agents, will be incorporated into active surveillance in the future remains to be seen. “Longer follow up is required to fully appreciate the biological significance of this approach,” says Goldenberg.

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