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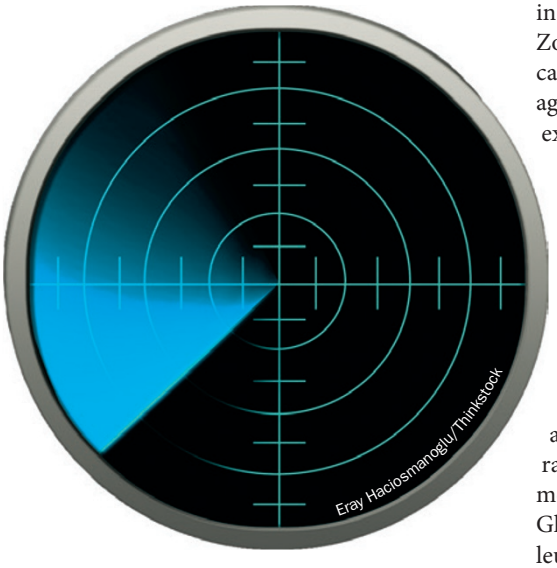
PROSTATE CANCER

Androgen suppression duration and zoledronic acid: under the RADAR

Each year, more than 5,000 men in Australia and New Zealand are diagnosed with locally advanced prostate cancer. Unfortunately, in at least 25% of cases, the cancer has metastasized to the bone and lymph glands that is undetectable by current imaging methods. As a result, these men cannot undergo observation and require treatment for prolonged periods. Although long-term androgen suppression following radiotherapy has been shown to be more effective than short-term androgen suppression (STAS), longer-term treatment is also associated with greater morbidities, such as osteopenia and fractures. The Trans-Tasman Radiation Oncology Group (TROG) 96.01 trial determined the value of 6 months of STAS. In the USA and Europe, androgen suppression lasting 28–36 months was frequently used after other trials showed that longer duration could reduce prostate cancer mortality. However, long-term and sometimes permanent side effects included sexual dysfunction, hot flushes, breast enlargement and pain, shrinkage of the genitalia, anaemia, blood clots, fatigue, cognitive dysfunction, depression and reductions in bone mineral density resulting in fractures.

"With these long-term testosterone suppression side effects in mind, we designed the TROG 03.04 RADAR trial to determine whether better outcomes could be achieved with intermediate-term androgen suppression (ITAS) and radiotherapy without all of these side effects," explains James Denham, lead investigator of the RADAR study. Since the bisphosphonate zoledronic acid has anti-cancer properties in men with castration-resistant prostate cancer and bone metastases, the RADAR trial was initiated to compare STAS with ITAS with or without zoledronic acid. This randomized, open-label, phase III trial



with a 2 × 2 factorial design enrolled 1,071 men with newly-diagnosed locally advanced prostate cancer. All men received 6 months of androgen suppression therapy (with leuprorelin) followed by radiotherapy. All men were then randomly allocated to either no further treatment or an extra 12 months of androgen suppression therapy and/or 18 months of zoledronic acid. Prostate cancer-specific mortality was the primary end point of the trial, and PSA progression was one of the secondary end points.

Denham summarizes the key findings: "For men with Gleason score 8–10 tumours who received ITAS (18 months in total) the interaction was highly beneficial for those who also received 18 months of zoledronic acid." Moreover, relapse rates were reduced by over 40% compared to the control arm. He continues, "however, for men with Gleason score tumours ≤7, zoledronic acid did not help. Of concern, those who received zoledronic acid and 6 months androgen suppression experienced a small but significant increase in bone metastases of approximately 1% per year. This effect was more pronounced in men with Gleason score ≤7 tumours. Zoledronic acid must therefore be used cautiously as a preventative measure against the development of metastases," explains Denham.

As these findings were based on secondary end point data from the trial, the authors point out that caution is needed when interpreting such data. External validation of the interaction between zoledronic acid and Gleason score is therefore needed. For men with Gleason score 8–10, 18 months of leuprorelin and zoledronic acid commencing 5 months before radiotherapy reduces metastatic spread by more than 40%. By contrast, in men with Gleason score ≤7 tumours, 18 months of leuprorelin may be the best option.

"We want to confirm the interaction between Gleason score and the use of zoledronic acid seen in the RADAR trial using a bone model because it could be very important from a biological perspective as well as the immediate clinical perspective," adds Denham. His team "is hoping to collaborate with other trialists evaluating the role of zoledronic acid in preventing prostate cancer bone metastasis, by conducting a meta-analysis that has exploration of the RADAR trial interaction as one of its goals."

Although further follow-up data from international trials are needed to establish the value of ITAS with or without zoledronic acid, the RADAR trial highlights that zoledronic acid benefits men at highest risk, but should be spared in men with Gleason score ≤7 tumours.

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Original article Denham, J. W. *et al*. Short-term androgen suppression and radiotherapy versus intermediate-term androgen suppression and radiotherapy, with or without zoledronic acid, in men with locally advanced prostate cancer (TROG 03.04 RADAR): an open-label, randomised, phase 3 factorial trial. *Lancet Oncol*. doi:10.1016/S1470-2045(14)70328-6