Effect of longer-interval versus standard dosing of zoledronic acid on skeletal events in patients with bone metastases. Himelstein AL, Foster JC, Khatcheressian JL et al. JAMA (2017) 317(1):48-58

Blog title

Three-monthly zoledronate is as good as monthly treatment

Expert's Summary

This phase III randomized controlled trial was designed to test whether 12-weekly zoledronate is non-inferior to 4-weekly zoledronate in terms of the risk of skeletal events. The study population comprised 1822 patients with metastatic bone disease from prostate cancer (38%), breast cancer or myeloma. No significant difference was seen in the proportion of patients having a skeletal event within 2 years; 29% versus 30% for 12-weekly versus 4-weekly treatment, respectively. The lower limit of the 95% confidence interval for the difference in risk was -4%, compared with the pre-specified non-inferiority margin of -7%, indicating that 12-weekly treatment is non-inferior to 4-weekly treatment.

Expert's opinion

Zoledronate has been widely used in men with metastatic castration-resistant prostate cancer (CRPC) to reduce the risk of skeletal-related events (SREs) (1). The optimum frequency of treatment is unknown, but less frequent treatment would of course be more convenient and economical. This trial provides good evidence that 12-weekly zoledronate is non-inferior to 4-weekly treatment. Furthermore, there was a trend towards a reduced risk of osteonecrosis of the jaw with less frequent treatment (1% versus 2%, p=0.08). The study included patients with three different primary cancers, but the results for men with prostate cancer were consistent with the overall results: the crude rate of SREs was 32% for 4-weekly treatment versus 30% for 12 weekly treatment.

In my view, this is a practice-changing study. Zoledronate for SRE prevention should no longer be given at 4-weekly intervals. Indeed, it is possible that the optimum interval could be longer than 12 weeks.

Denosumab may be used as an alternative to zoledronate for SRE prevention (2). The results of this trial highlight that the optimum frequency of denosumab treatment is also unknown. However, 12-weekly zoledronate is considerably cheaper, and arguably more convenient, than 4-weekly denosumab.

In recent years, abiraterone, enzalutamide and radium-223 have all been shown not only to improve overall survival but also to reduce the risk of SREs in men with CRPC. It is not known to what extent, if any, zoledronate or denosumab provide additional benefit. Increasingly, I believe we will use zoledronate or denosumab in men with CRPC not for preventing SREs, but rather for managing osteoporosis. In that case, treatment could be given at 12-month intervals (3).

References

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