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★ FEATURED

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Reduced Exposure Maintained Zoledronic Acids Therapeutic Effects to Treatment of Breast Cancer Patients With Bone Metastases

Lancet Oncol. 2013 May 15;[EPub Ahead of Print], D Amadori, M Aglietta, B Alessi, L Gianni, T Ibrahim, G Farina, F Gaion, F Bertoldo, D Santini, R Rondena, P Bogani, CI Ripamonti

TAKE-HOME MESSAGE

Results of a non-inferiority phase III Italian study, in which patients who had already received 1 year of bisphosphonate therapy were enrolled to receive zoledronic acid once every 12 weeks vs monthly, found the reduced exposure maintained the therapeutic effects of zoledronic acid.

ABSTRACT

Background: Zoledronic acid reduces skeletal-related events in patients with breast cancer, but concerns have been raised about prolonged monthly administration. We assessed the efficacy and safety of a reduced dosing frequency of zoledronic acid in women treated previously with monthly zoledronic acid.

Methods: We did this non-inferiority, phase 3 trial in 62 centres in Italy. We enrolled patients with breast cancer who had one or more bone metastases and had completed 12–15 months of monthly treatment with zoledronic acid. Patients were randomly assigned with a permutated block

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(size four to eight) random list stratified by centre in a 1:1 ratio to zoledronic acid 4 mg once every 12 weeks or once every 4 weeks, and followed up for at least 1 year. Neither patients nor investigators were masked to treatment allocation. The primary outcome was skeletal morbidity rate (skeletal-related events per patient per year) in the intention-to-treat population. We used a non-inferiority margin of 0·19. The trial is registered with EudraCT, number 2005-004942-15.

Findings: We screened 430 patients and enrolled 425, of whom 209 were assigned to the 12-week group and 216 to the 4-week group. The skeletal morbidity rate was 0·26 (95% CI 0·15–0·37) in the 12-week group versus 0·22 (0·14–0·29) in the 4-week group. The between-group difference was 0·04 and the upper limit of one-tailed 97·5% CI was 0·17, which is lower than the non-inferiority margin. The most common grade 3–4 adverse events were bone pain (56 [27%] patients in the 12-week group vs 65 [30%] in the 4-week group), nausea (24 [11%] vs 33 [15%]), and asthenia (18 [9%] vs 33 [15%]). Renal adverse events occurred in one patient (<1%) in the 12-week group versus two (1%) in the 4-week group. One patient (<1%) in the 4-week group had grade 1 acute renal failure. Osteonecrosis of the jaw occurred in four patients in the 12-week group versus three in the 4-week group. No treatment-related deaths were reported. Median N-terminal telopeptide concentration changed from baseline more in the 12-week group than in the 4-week group after 12 months (12·2% vs 0·0%; p=0·011).

Interpretation: Our results raise the possibility of decreasing administration of zoledronic acid to a 12-weekly regimen to reduce exposure during the second year, while maintaining its therapeutic effects. However, the effects on N-terminal telopeptide should be investigated further before changing current practice.

The Lancet Oncology

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