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[Intervention Review]

Bisphosphonates and other bone agents for breast cancer

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ABSTRACT

Background

Bone is the most common site of metastatic disease associated with breast cancer (BC). Bisphosphonates inhibit osteoclast-mediated bone resorption, and novel targeted therapies such as denosumab inhibit other key bone metabolism pathways. We have studied these agents in both early breast cancer and advanced breast cancer settings. This is an update of the review originally published in 2002 and subsequently updated in 2005 and 2012.

Objectives

To assess the effects of bisphosphonates and other bone agents in addition to anti-cancer treatment: (i) in women with early breast cancer (EBC); (ii) in women with advanced breast cancer without bone metastases (ABC); and (iii) in women with metastatic breast cancer and bone metastases (BCBM).

Search methods

In this review update, we searched Cochrane Breast Cancer's Specialised Register, CENTRAL, MEDLINE, Embase, the World Health Organization's International Clinical Trials Registry Platform (WHO ICTRP) and ClinicalTrials.gov on 19 September 2016.

Selection criteria

We included randomised controlled trials (RCTs) comparing: (a) one treatment with a bisphosphonate/bone-acting agent with the same treatment without a bisphosphonate/bone-acting agent; (b) treatment with one bisphosphonate versus treatment with a different bisphosphonate; (c) treatment with a bisphosphonate versus another bone-acting agent of a different mechanism of action (e.g. denosumab); and (d) immediate treatment with a bisphosphonate/bone-acting agent versus delayed treatment of the same bisphosphonate/bone-acting agent.

Data collection and analysis

Two review authors independently extracted data, and assessed risk of bias and quality of the evidence. The primary outcome measure was bone metastases for EBC and ABC, and a skeletal-related event (SRE) for BCBM. We derived risk ratios (RRs) for dichotomous outcomes and the meta-analyses used random-effects models. Secondary outcomes included overall survival and disease-free survival for EBC; we

derived hazard ratios (HRs) for these time-to-event outcomes where possible. We collected toxicity and quality-of-life information. GRADE was used to assess the quality of evidence for the most important outcomes in each treatment setting.

Main results

We included 44 RCTs involving 37,302 women.

In women with EBC, bisphosphonates were associated with a reduced risk of bone metastases compared to placebo/no bisphosphonate (RR 0.86, 95% confidence interval (CI) 0.75 to 0.99; P = 0.03, 11 studies; 15,005 women; moderate-quality evidence with no significant heterogeneity). Bisphosphonates provided an overall survival benefit with time-to-event data (HR 0.91, 95% CI 0.83 to 0.99; P = 0.04; 9 studies; 13,949 women; high-quality evidence with evidence of heterogeneity). Subgroup analysis by menopausal status showed a survival benefit from bisphosphonates in postmenopausal women (HR 0.77, 95% CI 0.66 to 0.90; P = 0.001; 4 studies; 6048 women; high-quality evidence with no evidence of heterogeneity) but no survival benefit for premenopausal women (HR 1.03, 95% CI 0.86 to 1.22; P = 0.78; 2 studies; 3501 women; high-quality evidence with no heterogeneity). There was evidence of no effect of bisphosphonates on disease-free survival (HR 0.94, 95% 0.87 to 1.02; P = 0.13; 7 studies; 12,578 women; high-quality evidence with significant heterogeneity present) however subgroup analyses showed a disease-free survival benefit from bisphosphonates in postmenopausal women only (HR 0.82, 95% CI 0.74 to 0.91; P < 0.001; 7 studies; 8314 women; high-quality evidence with no heterogeneity). Bisphosphonates did not significantly reduce the incidence of fractures when compared to placebo/no bisphosphonates (RR 0.77, 95% CI 0.54 to 1.08, P = 0.13, 6 studies, 7602 women; moderate-quality evidence due to wide confidence intervals). We await mature overall survival and disease-free survival results for denosumab trials.

In women with ABC without clinically evident bone metastases, there was no evidence of an effect of bisphosphonates on bone metastases (RR 0.96, 95% CI 0.65 to 1.43; P = 0.86; 3 studies; 330 women; moderate-quality evidence with no heterogeneity) or overall survival (RR 0.89, 95% CI 0.73 to 1.09; P = 0.28; 3 studies; 330 women; high-quality evidence with no heterogeneity) compared to placebo/no bisphosphonates however the confidence intervals were wide. One study reported a trend towards an extended period of time without a SRE with bisphosphonate compared to placebo (low-quality evidence). One study reported quality of life and there was no apparent difference in scores between bisphosphonate and placebo (moderate-quality evidence).

In women with BCBM, bisphosphonates reduced the SRE risk by 14% (RR 0.86, 95% CI 0.78 to 0.95; P = 0.003; 9 studies; 2810 women; high-quality evidence with evidence of heterogeneity) compared with placebo/no bisphosphonates. This benefit persisted when administering either intravenous or oral bisphosphonates versus placebo. Bisphosphonates delayed the median time to a SRE with a median ratio of 1.43 (95% CI 1.29 to 1.58; P < 0.00001; 9 studies; 2891 women; high-quality evidence with no heterogeneity) and reduced bone pain (in 6 out of 11 studies; moderate-quality evidence) compared to placebo/no bisphosphonate. Treatment with bisphosphonates did not appear to affect overall survival (RR 1.01, 95% CI 0.91 to 1.11; P = 0.85; 7 studies; 1935 women; moderate-quality evidence with significant heterogeneity). Quality-of-life scores were slightly better with bisphosphonates than placebo at comparable time points (in three out of five studies; moderate-quality evidence) however scores decreased during the course of the studies. Denosumab reduced the risk of developing a SRE compared with bisphosphonates by 22% (RR 0.78, 0.72 to 0.85; P < 0.001; 3 studies, 2345 women). One study reported data on overall survival and observed no difference in survival between denosumab and bisphosphonate.

Reported toxicities across all settings were generally mild. Osteonecrosis of the jaw was rare, occurring less than 0.5% in the adjuvant setting (high-quality evidence).

Authors' conclusions

For women with EBC, bisphosphonates reduce the risk of bone metastases and provide an overall survival benefit compared to placebo or no bisphosphonates. There is preliminary evidence suggestive that bisphosphonates provide an overall survival and disease-free survival benefit in postmenopausal women only when compared to placebo or no bisphosphonate. This was not a planned subgroup for these early trials, and we await the completion of new large clinical trials assessing benefit for postmenopausal women. For women with BCBM, bisphosphonates reduce the risk of developing SREs, delay the median time to an SRE, and appear to reduce bone pain compared to placebo or no bisphosphonate.

PLAIN LANGUAGE SUMMARY

Bisphosphonates and denosumab for breast cancer

What is the issue?

Breast cancer may spread and recur in the bones. This may cause fractures, pain and high calcium in the bloodstream (known as complications).

Medicines for osteoporosis may prevent these complications and may help cure cancer by reducing cancer growth in the bone. These medicines are called 'bisphosphonates'. A newer type is called ‘denosumab’. Bisphosphonates or denosumab are given in addition to other cancer treatment medications. These may be given along with chemotherapy, endocrine therapy, or radiotherapy.

Study questions

The goal of bisphosphonates and denosumab differs based on the women's breast cancer status.

We asked three main questions:

1. For **women with early breast cancer (EBC)**, can bisphosphonates or denosumab reduce the risk of the cancer spreading to the bone? Will adding this medicine to anticancer treatments allow women to live longer (improve survival)?

2. For **women with advanced breast cancer which does not appear to involve the bone (ABC)**, can bisphosphonates reduce the risk of the cancer spreading to the bone and improve survival? Will bisphosphonates reduce complications and improve quality of life?

3. For **women with metastatic breast cancer that has spread to the bone (BCBM),** can bisphosphonates or denosumab reduce the risk of complication, and improve quality of life and survival?

Study Results

We found 44 studies involving 37,302 participants. We included studies published by September 2016.

Study results for women with early breast cancer (EBC)

For women with EBC, we included 17 studies with 26,129 participants. The women's health was monitored for at least 12 months from the start of the study. Some studies monitored women for 10 years.

The studies tested different types of bisphosphonate drugs and denosumab, and different doses of these drugs. Some studies compared the drugs to no treatment. Some studies used oral medications. Other studies gave the medicine as an injection into a vein or under the skin.

Bisphosphonates probably lowered the risk of cancer spreading to the bone.

Bisphosphonates were found to improve survival, but the benefit in the whole group of women was small. Postmenopausal women had a benefit from bisphosphonates with improved survival and reduced risk of cancer returning. Premenopausal women did not have improved survival or reduced risk of the cancer returning. New studies that test bisphosphonates by the women's menopausal status are awaited.

We await the reporting of data on survival and other important outcomes from denosumab trials.

Study results for women with advanced breast cancer (ABC)

For women with ABC that had not spread to the bone, we included three studies enrolling 330 participants. All three studies compared oral bisphosphonates to no treatment.

Bisphosphonates did not reduce the risk of cancer spreading to the bone or improve survival. Very little information was available on complications and quality of life from only one study.

Study results for women with metastatic breast cancer that has spread to the bone (BCBM)

For women with BCBM, we included 24 studies enrolling 10,853 participants. Their health was monitored for at least 12 months. Some women were followed for 24 months. Most studies compared bisphosphonates to receiving no medication.

Bisphosphonates reduced complications (fractures and bone pain). Bisphosphonates did not appear to increase the length of time women survived. Quality of life scores were slightly better for women receiving bisphosphonates compared to similar women having no bisphosphonates.

Denosumab reduced the risk of complications compared to bisphosphonates in the three studies that collected these data. There was no benefit in survival from denosumab in the one study that collected data.

Side effects for women with all types of breast cancer

Side effects were uncommon and mild. There was a rare risk of damage to the jaw bone ("osteonecrosis of the jaw").

Quality of the evidence

Overall, most of the evidence was moderate to high-quality. This means that we are fairly confident in the findings.