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#### [Intervention Review]

# Bisphosphonates for advanced prostate cancer

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#### **ABSTRACT**

# **Background**

The prevalence and incidence of pain and skeletal complications of metastatic bone disease such as pathologic fractures, spinal cord compression and hypercalcemia is high and an important contributor to morbidity, poor performance status and decreased quality of life. Moreover, pathologic fractures are associated with increased risk of death in people with disseminated malignancies. Therefore, prevention of pain and fractures are important goals in men with prostate cancer at risk for skeletal complications.

# **Objectives**

To assess the effects of bisphosphonates in men with bone metastases from prostate cancer.

#### **Search methods**

We identified studies by electronic search of bibliographic databases including the Cochrane Controlled Trials Register and MEDLINE on 13 July 2017 and trial registries. We handsearched the *Proceedings of American Society of Clinical Oncology* (to July 2017) and reference lists of all eligible trials identified. This is an update of a review last published in 2006.

# **Selection criteria**

We included randomized controlled studies comparing the effectiveness of bisphosphonates in men with bone metastases from prostate cancer.

# **Data collection and analysis**

Two review authors independently extracted data and assessed the quality of trials. We defined the proportion of participants with pain response as the primary end point; secondary outcomes were skeletal-related events, mortality, quality of life, adverse events, analgesic consumption and disease progression. We assessed the quality of the evidence for the main outcomes using the GRADE approach.

#### **Main results**

We included 18 trials reporting on 4843 participants comparing the effect of bisphosphonate administration to control regimens.

**Primary outcome:** there was no clear difference in the proportion of participants with pain response (RR 1.15, 95% CI 0.93 to 1.43; P = 0.20;  $I^2 = 0\%$ ; 3 trials; 876 participants; low quality evidence). In absolute terms, bisphosphonates resulted in a pain response in 40 more participants per 1000 (19 fewer to 114 more).



**Secondary outcomes:** bisphosphonates probably reduced the incidence of skeletal-related events in participants with prostate cancer metastatic to bone (RR 0.87, 95% CI 0.81 to 0.94; P = 0.27;  $I^2 = 19\%$ ; 9 trials; 3153 participants; moderate quality evidence). In absolute terms, bisphosphonates resulted in 58 fewer SREs per 1000 (85 fewer to 27 fewer).

We found no clinically relevant differences in mortality (RR 0.97, 95% CI 0.91 to 1.04; P = 0.43;  $I^2 = 1\%$ ; 9 trials; 2450 participants; moderate quality evidence). In absolute terms, bisphosphonates resulted in 16 fewer deaths per 1000 (47 fewer to 21 more).

Outcome definition of quality of life and the measurement tools varied greatly across trials and we were unable to extract any quantitative data for meta-analysis.

Bisphosphonates probably increased the number of participants affected by nausea (RR 1.19, 95% CI 1.00 to 1.41; P = 0.05;  $I^2 = 0\%$ ; 9 trials; 3008 participants; moderate quality evidence). In absolute terms, bisphosphonates resulted in seven more cases of nausea per 1000 (0 fewer to 14 more). Bisphosphonates probably increased the number of renal adverse events (RR 1.65, 95% CI 1.11 to 2.46; P = 0.01;  $I^2 = 0\%$ ; 7 trials; 1794 participants; moderate quality evidence). In absolute terms, bisphosphonates resulted in 22 more renal adverse events per 1000 (4 more to 50 more). We found no clear difference in the number of participants with osteonecrosis of the jaw between groups (RR 1.92, 95% CI 0.75 to 4.90; P = 0.17;  $I^2 = 0\%$ ; 5 trials; 1626 participants; very low quality evidence). In absolute terms, bisphosphonates resulted in seven more cases with osteonecrosis of the jaw per 1000 (2 fewer to 29 more). We observed no clinically relevant difference in the proportion of participants with decreased analgesic consumption (RR 1.19, 95% CI 0.87 to 1.63; P = 0.28;  $I^2 = 37\%$ ; 4 trials; 416 participants). Statistical analysis revealed that bisphosphonates probably reduced the number of participants with disease progression (RR 0.94, 95% CI 0.90 to 0.98; P = 0.006;  $I^2 = 0\%$ ; 7 trials; 2115 participants; moderate quality evidence). In absolute terms, bisphosphonates resulted in 36 fewer cases of disease progression per 1000 (71 fewer to 7 fewer).

Findings of our predefined subgroup and sensitivity analyses were no different from those of the primary analyses.

#### **Authors' conclusions**

Based on low quality evidence, there may be no clinically relevant difference in the proportion of men with pain response between bisphosphonates and control regimens in men with bone metastases from prostate cancer. Bisphosphonates probably decrease the number of skeletal-related events and disease progression. These benefits need to be weighed against the increased risk of renal impairment and nausea in men receiving bisphosphonates. Future studies should explicitly evaluate patient important outcomes such as quality of life and pain by using standardized and comparable assessment tools.

#### PLAIN LANGUAGE SUMMARY

## Bisphosphonates for advanced prostate cancer

# **Review question**

This review and analysis compared the chance of pain reduction, number of bone complications (skeletal-related events), number of deaths, quality of life, side effects, use of analgesics (pain killers) and progression of cancer in men with bone metastases (bone cancer) from prostate cancer.

# **Background**

The prostate is a gland in the male reproductive system. Prostate cancer can spread to other parts of the body (called metastases) including the bones. Bone fractures and compression of the spinal cord are feared complications in addition to death due to prostate cancer. Bisphosphonates are medicines that interact with the formation of new bone and might be useful to prevent the men from experiencing bone pain, fractures or other skeletal complications. We focused this review on pain because pain frequently occurs and can restrict the daily life activities and might require further treatment.

# **Study characteristics**

We searched medical databases to 13 July 2017. Two review authors independently screened, summarized and analyzed the findings. This led to the inclusion of 18 clinical trials.

# **Key results**

We found low quality evidence that bisphosphonates provided no clinically relevant difference in pain response (three studies involving 876 men) compared to placebo (pretend treatment) or no additional treatment. Bisphosphonates reduced pain in 40 more men per 1000 men (19 fewer to 114 more).

We found moderate quality evidence that bisphosphonates probably resulted in 58 fewer skeletal-related events per 1000 (85 fewer to 27 fewer). Bisphosphonates showed no clear difference in the number of men who died or the number of men with decreased use of pain killers. We observed moderate quality evidence that bisphosphonates probably increased the number of men with nausea. Bisphosphonates resulted in seven more men with nausea per 1000 men (0 fewer to 14 more). We found moderate quality evidence that



bisphosphonates probably increased the number of men with kidney problems. In this case, bisphosphonates resulted in 22 more men with renal complications per 1000 men (4 more to 50 more). For osteonecrosis of the jaw (where the jaw bone weakens and dies), we found very low quality evidence that bisphosphonates showed no clear difference. We observed moderate quality evidence that bisphosphonates probably decreased the number of men affected by disease progression (where the disease got worse). This means that bisphosphonates resulted in 36 fewer men with disease progression per 1000 men (71 fewer to 7 fewer). We found no useable data on quality of life.

# Quality of the evidence

We judged the quality of evidence as moderate to very low.