# Effect of bisphosphonates on pain and quality of life in patients with bone metastases

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## SUMMARY

**Bone is the most common organ for tumor metastasis, especially in patients with cancers of the breast or prostate. Bone metastases disrupt skeletal metabolism and result in considerable skeletal morbidity, including intractable, chronic bone pain, hypercalcemia of malignancy, pathologic fracture and spinal-cord compression. In addition to the chronic pain caused by bone metastases, skeletal-related events (SREs) such as pathologic fractures and spinal-cord compression can result in acute increases in pain. These effects can severely impair mobility and contribute to a general decrease in quality of life. Palliative options to treat bone metastases include radiotherapy, analgesics, surgery and bisphosphonates. These drugs bind to the surface of the bone and impair osteoclast-mediated bone resorption, and reduce the tumor-associated osteolysis that is initiated by the development of skeletal metastases. In addition to preventing SREs, bisphosphonates can palliate bone pain caused by a variety of solid tumors. This Review summarizes the clinical trial data of bisphosphonates for the prevention of SREs and the palliation of bone pain. Among these agents, nitrogen-containing bisphosphonates are recognized as the most effective, and zoledronic acid has demonstrated the broadest clinical utility.**

**KEYWORDS bisphosphonates, bone metastases, bone pain, quality of life, zoledronic acid**

### REVIEW CRITERIA

The PubMed and MEDLINE databases were searched for articles published until 31 December 2007. The search terms included "bone metastases" in association with other search terms: "bone pain," "breast cancer," "prostate cancer," "lung cancer," "multiple myeloma," "bisphosphonate," "skeletal-related events," and "quality of life." When possible, primary sources have been quoted. Full articles were obtained in most cases and references were checked for additional material when appropriate. References were chosen on the basis of the best clinical or laboratory evidence.

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## INTRODUCTION

Therapeutic advances in the field of oncology have greatly extended the survival of patients with a variety of malignancies. An emerging challenge in oncology is, therefore, the preservation of quality of life (QOL) and functional independence throughout a patient's lifetime. Bone is the most common site for tumor metastasis, and bone metastases are especially common in patients with breast or prostate cancer. Tumor cells that infiltrate the bone can disrupt bone metabolism, and typically lead to osteoclast stimulation. Increased levels of osteoclast-mediated osteolysis can severely weaken the structural integrity of bone and result in painful and potentially debilitating skeletal-related events (SREs). These events include bone pain that requires palliative radiotherapy, hypercalcemia of malignancy, pathologic fracture, the requirement for orthopedic surgery, and spinal-cord compression.[1,2] SREs occur in approximately 50% of patients with bone metastases;[3] they can be life-limiting (i.e. impair QOL and shorten survival time) and might result in significant loss of physical function. For example, the majority of pathologic fractures will not heal without surgical intervention, radiotherapy, or both these treatments.[4]

Bone metastases can have chronic effects on patients, and can reduce their functional capacity and undermine their QOL. For example, pain may result when the tumor disrupts tissue during invasion or when it causes pressure on nerve endings.[5] Bone metastases can activate pain receptors in affected bone and are the most common source of cancer-associated pain.[6–8] Although bisphosphonates offer many benefits to patients with bone lesions, QOL changes are difficult to assess with currently available tools. Evidence exists that various bisphosphonates can prevent skeletal morbidity and these agents are used for the treatment of bone pain in patients with advanced malignancies. We discuss the great promise that many of these agents, in particular nitrogen-containing bisphosphonates, have demonstrated in this setting.

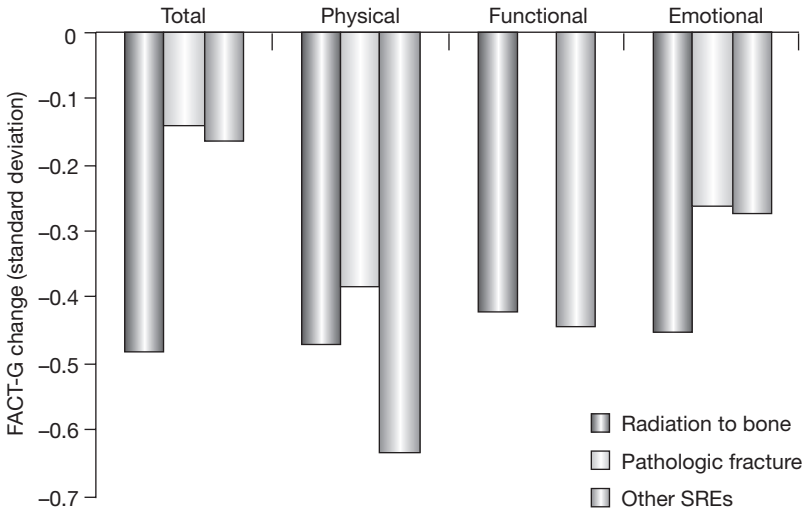


**Figure 1** Skeletal complications reduce quality of life in patients with bone metastases from prostate cancer. Change in FACT-G scores for patients with an SRE compared to patients without an SRE. Reprinted with permission from Elsevier © Weinfurt K *et al.* (2005) *Ann Oncol* **16:** 579–584;[10] reprinted from Kinnane N (2007) *Eur J Oncol Nurs* **11 (Suppl 2):** S28–S31.[11] Abbreviations: FACT-G, Functional Assessment of Cancer Therapy–General; SRE, skeletal-related event.

## QUALITY OF LIFE ASSESSMENT

Bone pain and SREs can undermine QOL and compromise patients' functional independence.[9] Each type of SRE has been associated with decreases in multiple aspects of patients' QOL (Figure 1).[10,11] Furthermore, loss of the ability to participate in daily activities, and hindrance of an individual's ability to take care of his or her personal hygiene can lead to anxiety and depression.[12] Clinical trial assessments, however, have focused primarily on frequency of SREs instead of less-quantitative measures such as pain, loss of functional independence, and QOL. Bone pain is a frequent symptom of bone metastases in patients with advanced cancer, and bone pain has been an end point studied in many clinical trials that have investigated the use of bisphosphonates. The correlation between pain and decreased QOL suggests that bone pain measurements might be used as a surrogate for health-related QOL in patients with malignant bone disease.[13]

Currently, the most common tools used to assess functional status include the Brief Pain Inventory,[14] which is a general pain instrument with a scale of 1–10 that includes assessments for the ability to walk and to perform work, and the visual analog scale, which measures pain across a continuum. In addition, FACT-G[15] (Functional Assessment of Cancer Therapy—General; a QOL scale) assessments include measurements of physical well-being and the ability to perform everyday tasks. Many of the tools used to assess health-related QOL in patients with cancer do not specifically address the multidimensional consequences of SREs on QOL in patients with metastatic bone disease, and limited data are available in this setting. Examples of such health-related QOL assessment tools include Spitzer QL-index,[16] European Organisation for Research and Treatment of Cancer Quality of Life Core Questionnaire 30 (EORTC QLQ-C30),[17] and EQ-5D (EuroQoL 5 Dimensions).[18]

The Bone Metastases Quality-of-Life questionnaire (BOMET-QoL) and the BM-22 module of the EORTC QLQ-C30 have been designed to assess the skeletal complications and bone pain that affect the QOL of patients with metastatic bone disease.[19–21] Similar to other tools that use patient-reported outcomes to assess QOL, the BOMET-QoL is a simple, self-administered questionnaire composed of 10 questions that can be used to monitor patients' QOL status, including their mobility and functional impairment. Questions are designed to assess common dimensions of QOL for patients with bone metastases, as well as to determine whether patients experience pain that is typical of the disease (e.g. intense, constant) and whether pain is localized to common sites of metastases (e.g. spine, pelvic bone, proximal femur). The EORTC QLQ-BM22, a bone-metastasis-specific tool, is being developed for use in the clinical trial setting to address QOL dimensions that are relevant across multiple cancer types and treatment modalities for the management of malignant bone disease.[20] This system uses a 4-point scale to assess loss of mobility, adverse effects, complications of treatment, and patients' concerns about dependency. Data that emerge from the use of these tools in the clinical trial setting will increase insight into the direct effects of SREs on the health-related QOL of patients with metastatic bone disease, and could help to optimize the care of patients in this setting.

## TREATMENT OPTIONS FOR PATIENTS WITH BONE METASTASES

Many strategies have been used to treat skeletal complications and to manage chronic bone pain in patients with malignant bone disease. Traditional strategies were developed to treat bone pain or skeletal fractures. These approaches include radiation therapy (including radionuclide therapy), analgesia and surgery.[22] These strategies, however, do not

address the underlying cause of skeletal complications (i.e. increased bone resorption) and are not effective in the prevention of SREs. Antiresorptive agents such as bisphosphonates target the cause rather than consequences of SREs, and are effective in the prevention of these events.

### Treatment of SREs

With the advent of bisphosphonate therapy, physicians are now able to prevent or delay the onset of SREs.[23,24] Bisphosphonates bind to the surface of the bone, are taken up by osteoclasts during osteolysis, and can induce apoptosis of osteoclasts.[25] Bisphosphonates reduce osteoclast viability and function, and, therefore, decrease the abnormally high levels of bone resorption that are characteristic of malignant bone disease. Bisphosphonates have also shown antitumor activity in the preclinical setting in several cancer cell lines including lung, breast, and prostate cancer.[26–30] In patients with bone metastases, the goal of bisphosphonate therapy is to prevent the onset and recurrence of SREs, and to palliate bone pain, which could reduce the need for analgesics and palliative therapies such as surgery and radiation to the bone. Bisphosphonates offer several advantages over other localized therapies. Unlike external-beam radiotherapy, bisphosphonates are not limited to an anatomic site but are dispersed systemically and attach rapidly to mineralized bone surfaces.[25,31,32] Indeed, blood flow—and hence, delivery of these agents—can be increased at sites of active bone remodeling.[33] Bisphosphonates can also be used in combination with other anticancer treatments, such as chemotherapy, without an associated increase in myelotoxicity, which is a well known side-effect of cytotoxic chemotherapy. Notably, data from preclinical studies have demonstrated synergistic effects of combining zoledronic acid (and to a lesser extent other bisphosphonates)[34] with various chemotherapeutic regimens, and preliminary clinical studies suggest that such regimens are feasible.[35–39] For example, combined treatment with docetaxel and zoledronic acid resulted in an additive and synergistic decrease in the viability of prostate cancer cells *in vitro*.[39] In a pilot study in 25 patients with hormone-refractory prostate cancer, combination therapy with weekly docetaxel and zoledronic acid every 4 weeks elicited a clinical response in 58% of patients.[37] Other small studies suggest that such antitumor activity might also include inhibition of angiogenesis (i.e. through a reduction in circulating levels of vascular endothelial growth factor), immunostimulatory effects (through the induction of γδ T-cell proliferation), and reduction of disseminated tumor cells in the bone marrow.[40]

### Palliation of bone pain

Pharmacotherapy for metastatic bone pain that is generally moderate to severe in nature, consists of long-term administration of NSAIDs or paracetamol (acetaminophen), along with potent opioid analgesics. Opioids, in conjunction with adjuvant analgesics, provide effective palliation in many cases, particularly in patients with vertebral metastases. Opioids, however, are associated with considerable drug-related adverse effects that can negatively affect patients' QOL.[41,42] In addition to the potential for addiction, a common adverse effect from opioid use is sedation, which can limit functional autonomy in patients with life expectancies of several months or years. Opioids can also cause respiratory depression, which is rare, but potentially lethal.[41] In a study of patients with metastatic prostate cancer, a third of those who died were in an opioid-induced coma at the time of death and had no other discernable cause of death at autopsy.[43] Patients' QOL can also be affected by obstructive bowel disorders that result from the most common adverse effect of opioids, constipation.[44] Furthermore, management of these adverse effects requires careful dose titration of opioids, and the best-tolerated dose might not provide optimal analgesia.

Pain from bone metastases that is not manageable with analgesics is typically treated with radiation therapy.[45] Although most patients with painful bone metastases are likely to benefit from radiation therapy, precise data on the proportion of patients who actually receive such treatment are not available. One report, however, suggests that radiation therapy might be underused because of the inconvenience of multiple visits for both planning and treatment.[46] For localized bone pain, a randomized, controlled trial demonstrated that external-beam radiation therapy (EBRT) can reduce pain in up to 50% of patients.[47] The optimum fraction dosing and total doses of EBRT required for pain relief have not yet been established. Pain palliation can have a delayed onset, and up to 16% of patients who undergo EBRT experience pain flares after treatment.[48] EBRT, therefore, might not be appropriate in patients with short life expectancy. In addition, the toxicity of EBRT can limit its value for patients with multiple or diffuse lesions. For these patients,

**Table 1** Summary of trials that investigated early-generation bisphosphonates.

| Reference | Patients (*n*) | Tumor type | Drug regimen | Comparator | Efficacy results |
|---|---|---|---|---|---|
| **Etidronate** | | | | | |
| Iwamoto *et al.* (2002)[53] | 30 | Several | 400 mg per day orally for 2 weeks | Baseline | Transient decrease in pain |
| **Clodronate** | | | | | |
| Heidenreich *et al.* (2001)[54] | 85 | Prostate cancer | 300 mg per day intravenously for 8 days, followed by 1,600 mg per day orally | Baseline | Decrease in pain vs baseline (VAS 7.9 to 2.5; $P<0.001$)<br>Increased Karnofsky PS vs baseline (45% to 70%; $P$=NR) |
| Tubiana-Hulin *et al.* (2001)[55] | 144 | Breast cancer | 1,600 mg per day orally | Placebo | Decrease in pain ($P=0.01$)<br>Increased time to first SRE ($P=0.05$) |
| Ernst *et al.* (2003)[56] | 209 | Prostate cancer | 1,500 mg intravenously every 3 weeks | Placebo | No change in pain, survival, QOL, or palliative response ($P$=NS) |
| Santangelo *et al.* (2006)[57] | 35 | Several | 300 mg intravenously every 2 days | Baseline | Significant decrease in pain<br>Significant increase in QOL ($P$=NR) |
| Ozyuvaci *et al.* (2005)[58] | 16 | Prostate cancer | 400 mg orally three times a day | No bisphosphonate treatment | Decrease in pain (75% vs 66% without bisphosphonate; $P<0.0001$) |
| Donat *et al.* (2005)[59] | 176 | Breast cancer | 2 × 400 mg per day orally | Baseline | Significant decrease in pain (VAS 8 to 4; $P$=NR)<br>Increased Karnofsky PS (60% to 80%; $P$=NR) |
| Rodrigues *et al.* (2004)[60] | 58 | Prostate cancer | 1,500 mg intravenously every 28 days, then every 4–6 months | Baseline | Decreased mean pain scores (VAS 7.4 to 2.4)<br>Increased Karnofsky PS (43% to 73%; $P$=NR) |
| Hering *et al.* (2003)[61] | 32 | Prostate cancer | 1,500 mg intravenously every 28 days | Baseline | Decrease in pain in 91% of patients (VAS 7.7 to 2.1)<br>Increased Karnofsky PS (42% to 71%) |

Abbreviations: NR, not reported; NS, not significant ($P>0.05$); PS, performance status; QOL, quality of life; SRE, skeletal-related event; VAS, visual analog scale (10 point).

systemic administration of radionuclide therapy might be effective. Indeed, reductions in mean pain levels have been reported after radionuclide therapy in approximately 70% of patients with prostate or breast cancer.[49] Although this therapy can provide effective palliation of bone pain, little is known about the effects of radiation on the structural integrity of the skeleton, which is an important consideration in a weight-bearing site (e.g. pelvis, femur, and tibia). Moreover, radionuclide therapy is associated with temporary, dose-limiting myelosuppression.[50] Although generally reversible, recovery from such myelosuppression is dependent on existing bone marrow reserve, which is often low in patients undergoing cytotoxic chemotherapy for metastatic cancer.

Patients with bone metastases can sometimes require orthopedic surgery to treat or prevent an impending pathologic fracture. Surgery is especially common in patients who have osteolytic lesions on weight-bearing bones. This intervention results in additional costs to the patient, and can lead to extended convalescence and rehabilitation.[51]

## EVIDENCE FOR EFFICACY OF BISPHOSPHONATES IN PAIN MANAGEMENT

### Early-generation bisphosphonates

Early-generation bisphosphonates (e.g. sodium clodronate, disodium etidronate) have been established as effective palliative therapy in patients with malignant bone disease. These bisphosphonates are metabolized by osteoclasts to produce nonhydrolyzable, cytotoxic ATP analogs, which result in loss of mitochondrial membrane potential and direct induction of apoptosis. The high affinity of bisphosphonates for the bone ensures the selective accumulation of cytotoxic metabolites within osteoclasts.[52] These agents, however, have a limited effect (Table 1)[53–61] and have only been tested in a few tumor types. For example, in patients with bone metastases from a variety of tumors, oral etidronate 400 mg daily for 2 weeks reduced bone pain levels compared with baseline; however, this effect was transient and had diminished after 12 weeks.[53] The introduction of clodronate provided physicians with a slightly more active alternative to etidronate. In a randomized trial of 144 patients with breast cancer, oral clodronate

1,600 mg daily, in addition to chemotherapy or hormonal therapy, provided significant palliation of pain compared with placebo ($P=0.01$, measured using a visual analog pain scale) and significantly delayed the median time to first SRE compared with placebo ($P=0.05$).[55] In a study of 85 patients with prostate cancer, after an initial 8-day period on a starting dose of 300 mg daily, the same dose and schedule (i.e. 1,600 mg daily) significantly reduced pain below baseline levels ($P<0.001$), reduced analgesic use, and improved Karnofsky performance status.[54] Intravenous monthly clodronate therapy, however, failed to provide significant pain palliation in combination with standard therapy in patients with hormone-refractory prostate cancer in two randomized, double-blind, placebo-controlled trials.[56,62] Clodronate is currently not approved for intravenous use. These data, although promising, were inconsistent and suggest that clear efficacy of clodronate for pain control has not been demonstrated.

### Nitrogen-containing bisphosphonates

In contrast to the early-generation bisphosphonates, nitrogen-containing bisphosphonates affect osteoclast activity and survival by inhibiting the enzyme farnesyl diphosphate synthase. This inhibition interferes with a variety of cellular functions that are essential for the bone-resorbing activity and survival of osteoclasts.[52] The nitrogen-containing bisphosphonates include disodium pamidronate, alendronic acid, ibandronate sodium, risedronate sodium, and zoledronic acid. The introduction of these agents in the clinical trial setting resulted in dramatically improved therapeutic activity (Table 2 [an enlarged version of Table 2 that includes information on additional studies is available online]).[63–78]

Pamidronate was among the first nitrogen-containing bisphosphonates introduced. Its efficacy as a therapeutic agent for patients with bone metastases has been studied in a variety of cancers. In one study, the efficacy of pamidronate was compared with that of placebo in 382 patients with breast cancer and osteolytic bone metastases.[63] This study demonstrated that 90 mg pamidronate increased the median time to a first SRE by approximately 6 months compared with placebo ($P=0.005$), and decreased the proportion of patients with skeletal complications by 13% ($P=0.008$). In addition, patients treated with pamidronate had a smaller increase in bone pain than placebo-treated patients ($P=0.046$) after 12 months of treatment.[63] The study was extended for an additional year and the number of patients with SREs at the end of 24 months was significantly lower with pamidronate than with placebo ($P<0.001$), but no significant differences in QOL, survival, or performance status were reported.[64] However, data from long-term follow-up of patients enrolled in these trials demonstrated effective palliation of bone pain by pamidronate in women with osteolytic lesions from breast cancer. Pamidronate-treated patients had a significant decrease in pain scores (–0.07 versus +1.14 units on a scale that combined pain intensity and frequency, $P=0.015$) and analgesic use (–0.06 versus +1.84 on a scale that combined type of analgesic used with frequency of use, $P<0.001$) compared with patients who received placebo.[79] Although Eastern Cooperative Oncology Group (ECOG) performance status and overall QOL deteriorated in all patients, pamidronate treatment was associated with a trend toward less deterioration (ECOG status change 0.29 versus 0.52, $P=0.133$; Spitzer QOL index change –0.57 versus –0.97, $P=0.211$).

Pamidronate has also been studied in patients with bone metastases secondary to prostate cancer; however, it produced no significant benefits compared with placebo in the incidence of SREs or the severity of bone pain, and pamidronate is currently not indicated in this setting.[66] In a meta-analysis of two multicenter, double-blind, randomized, placebo-controlled trials of 378 patients with bone pain from metastatic prostate cancer, no sustained significant differences were observed between pamidronate and placebo groups in self-reported pain measurements, analgesic use, proportion of patients with an SRE, or mobility.[66]

Ibandronate is a relatively new nitrogen-containing bisphosphonate that has demonstrated greater potency than pamidronate in animal studies.[52] In patients with bone metastases from breast cancer, 6 mg intravenous ibandronate significantly reduced the frequency of SREs by 20% compared with placebo ($P=0.004$), and reduced the number of new bone events per patient by 27% versus placebo ($P=0.032$).[71] This therapeutic agent can also be administered orally. A pooled analysis of two phase III trials in patients with breast cancer and bone metastases demonstrated that 50 mg oral ibandronate reduced the risk of developing SREs by 38% ($P<0.0001$), and reduced the frequency of new bone events by 14% ($P=0.041$).[80] Notably, these results reached significance only when the results of the two trials were pooled. In another randomized,

**Table 2** Summary of trials that investigated nitrogen-containing bisphosphonates (other than zoledronic acid).

| Reference | Patient (*n*) | Tumor type | Drug regimen | Comparator | Efficacy results |
|---|---|---|---|---|---|
| **Disodium pamidronate** | | | | | |
| Hortobagyi *et al.* (1996)[63] | 382 | Breast cancer | 90 mg intravenously every 4 weeks for 12 months | Placebo | Decreased SRE ($P=0.008$)<br>Increased time to first SRE ($P=0.005$)<br>Decreased VAS pain scores (44% vs 32%; $P=0.03$) |
| Theriault *et al.* (1999)[65] | 372 | Breast cancer | 90 mg intravenously every 4 weeks for 24 months | Placebo | Decreased SRE ($P=0.027$)<br>Decreased SMR ($P=0.008$) |
| Small *et al.* (2003)[66] | 378 | Prostate cancer | 90 mg intravenously every 3 weeks for 27 weeks | Placebo | Increased pain[a] ($P=$NS)<br>Decreased SRE ($P=$NS) |
| Groff *et al.* (2001)[68] | 200 | Several | 60 mg per week intravenously for 3 weeks, then every 3 weeks for 18 months | Baseline | Stable Karnofsky PS |
| **Ibandronate sodium** | | | | | |
| Body *et al.* (2004)[70] | 564 | Breast cancer | 50 mg per day orally for up to 96 weeks | Placebo | Decreased pain[a] (Change from baseline –0.1 vs +0.2; $P=0.001$) |
| Body *et al.* (2003)[71] | 466 | Breast cancer | 2 mg or 6 mg intravenously every 3–4 weeks for up to 24 months | Placebo | Decreased pain[a] ($P=$NR)<br>Decreased SMPR ($P=0.004$) |
| Tripathy and Bergström (2005)[72] | 876 | Breast cancer | 6 mg intravenously every 3–4 weeks or 50 mg orally | Placebo | Decreased pain[a] (for 6 mg intravenously, change from baseline –0.28 vs +0.21; $P<0.001$) |
| Menssen *et al.* (2002)[73] | 198 | Multiple myeloma | 2 mg per month intravenously for 12–24 months | Placebo | Decreased SRE ($P=$NS)<br>Increased survival ($P=$NS) |
| Tripathy *et al.* (2004)[74] | 435 | Breast cancer | 50 mg per day orally | Placebo | Decreased SMPR (18%, $P=0.037$)<br>Decreased RR of SRE ($P=0.005$) |
| Body *et al.* (2005)[75] | 383 | Several | 6 mg intravenously every 3–4 weeks ($n=312$); 4 mg intravenously for 4 days ($n=18$); 6 mg intravenously for 3 days, then every 4 weeks ($n=53$) | Placebo | Decreased pain[a] (change from baseline –0.28 vs +0.21; $P<0.001$)<br>Increased QOL ($P=$NR) |

[a]Pain was assessed on a 5-point scale. This table only includes data from studies involving more than 100 patients. An enlarged version of this table is available as Supplementary Table 2 on the *Nature Clinical Practice Oncology* website. Abbreviations: NS, not significant ($P>0.05$); NR, not reported; PS, performance status; QOL, quality of life; RR, relative risk; SMR, skeletal morbidity rate; SMPR, skeletal morbidity period rate; SRE, skeletal-related event; VAS, visual analog scale.

double-blind, placebo-controlled trial, patients with breast cancer and bone metastases who were treated with 20 mg or 50 mg oral ibandronate also experienced a significant decrease in the frequency of SREs versus placebo ($P=0.024$ and $P=0.037$, respectively).[74] Moreover, the relative risk of skeletal events was reduced by 38% (20 mg dose, $P=0.009$) and 39% (50 mg dose, $P=0.005$) compared with placebo. Mean patient-reported bone pain scores increased by 0.21 in the placebo group, compared with a slight increase of 0.03 in the 50 mg group ($P=0.201$), and a decrease of 0.06 in the 20 mg group ($P=0.071$). These changes reflect a 17% increase (placebo), a 4.5% decrease (20 mg ibandronate), and a 2.3% increase (50 mg ibandronate) in mean pain scores compared with respective baseline levels.

Overall, ibandronate treatment has produced trends toward decreased pain, but the magnitude of improvement in pain scores has been inconsistent. Similarly, the effect of ibandronate on QOL is not well characterized. QOL analyses of the results from the two pooled phase III trials of oral ibandronate described above revealed less deterioration in QOL (–8.3 versus –26.8 on a 100-point scale, $P=0.032$) with ibandronate treatment compared with placebo.[70] Ibandronate treatment also reduced pain scores and maintained them significantly below baseline throughout the study duration of 96 weeks in these analyses (–0.1 versus +0.2 on a 5-point scale, $P=0.001$ versus placebo). Ibandronate, however, has not been well studied in patients with bone metastases secondary to solid tumors other than breast cancer. One small study that assessed the efficacy of combined radiotherapy and ibandronate for treatment of bone metastases from various solid tumors (breast, prostate, lung, and renal) reported a 4.28 point increase in

**Table 3** Summary of randomized clinical trials of 4 mg zoledronic acid.

| Reference | Patient (*n*) | Tumor type | Regimen | Comparator | Efficacy results |
|---|---|---|---|---|---|
| Vogel *et al*. (2004)[81] | 638 | Several | 4 mg every 3–4 weeks for 6 doses | Baseline | Decreased pain (–6.9 on VAS; $P<0.05$) |
| Kohno *et al*. (2005)[82] | 228 | Breast cancer | 4 mg every 4 weeks for 1 year | Placebo | Decreased SRE ($P=0.027$)<br>Decreased RR SRE ($P=0.019$) |
| Saad *et al*. (2002)[83] | 643 | Prostate cancer | 4 mg every 3 weeks for 15 months | Placebo | Decreased SRE ($P=0.021$)<br>Increased time to first SRE ($P=0.011$) |
| Saad *et al*. (2004)[24] | 122[a] | Prostate cancer | 4 mg every 3 weeks for 24 months | Placebo | Decreased SRE ($P=0.005$)<br>Decreased RR SRE ($P=0.002$)<br>Reduced BPI scores (0.58 vs 1.05; $P<0.024$) |
| Weinfurt *et al*. (2006)[84] | 422 | Prostate cancer | 4 mg every 3 weeks for up to 15 months | Placebo | Decreased pain BPI ($P=0.04$) |
| Rosen *et al*. (2003)[85] | 773 | Lung cancer and other solid tumors | 4 mg every 3 weeks for 9 months | Placebo | Decreased SRE ($P=$NS)<br>Increased time to first SRE ($P=0.023$)<br>Decreased RR SRE ($P=0.017$) |
| Rosen *et al*. (2004)[86] | 773[b] | Lung cancer and other solid tumors | 4 mg every 3 weeks for 21 months | Placebo | Decreased SRE ($P=$NS)<br>Increased time to first SRE ($P=0.009$)<br>Decreased annual incidence of SREs ($P=0.012$)<br>Decreased RR SRE ($P=0.003$) |
| Rosen *et al*. (2001)[87] | 1,648 | Breast cancer<br>Multiple myeloma | 4 mg every 3–4 weeks for 12 months | Disodium pamidronate 90 mg intravenously every 3–4 weeks | Decreased pain BPI ($P=$NS)<br>Decreased SMR (in those who also received EBRT; $P=0.018$) |
| Rosen *et al*. (2004)[88] | 1,648[c] | Breast cancer<br>Multiple myeloma | 4 mg every 3–4 weeks for 24 months | Disodium pamidronate 90 mg intravenously every 3–4 weeks | Decreased RR for SREs ($P=0.030$) |
| Rosen *et al*. (2004)[88] | 766 | Breast cancer | 4 mg every 3–4 weeks for 12 months | Disodium pamidronate 90 mg intravenously every 3–4 weeks | Decreased RR for SREs ($P=0.037$)<br>Increased time to first SRE ($P=0.013$) |
| Wardley *et al*. (2005)[89] | 101 | Breast cancer | 4 mg every 3 weeks for up to 27 weeks | Baseline | Decreased worst, average, and interfering pain (change in baseline from –0.5 to –0.8 overall BPI score; $P<0.04$ in last 7 days) |
| Wiktor-Jedrzejczak (2005)[90] | 260 | Several | 4 mg every 3–4 weeks for up to 24 weeks | Baseline | Decreased pain (–20.9 on VAS; $P<0.001$)<br>Increased QOL FACT-G score ($P<0.001$) |

[a]This study was an extension of Saad *et al.* (2003).[83] [b]This study was an extension of Rosen *et al.* (2003).[85] [c]This study was an extension of Rosen *et al.* (2001).[87] This table only includes data from studies involving more than 100 patients. An enlarged version of this table is available as Supplementary Table 3 on the *Nature Clinical Practice Oncology* website. Abbreviations: BPI, Brief Pain Inventory; EBRT, external beam radiation therapy; FACT-G, Functional Assessment of Cancer Therapy-General; NS, not significant ($P>0.05$); QOL, quality of life; RR, relative risk; SMR, skeletal morbidity rate; SRE, skeletal-related event; VAS, visual analog scale (100 point).

EORTC-QOL scores, and a 19.6 point increase in Karnofsky performance status (on a 100-point scale) versus baseline.[77] This study, however, did not include patients who received radiotherapy alone, so whether this improvement is attributable to ibandronate is unclear. A pilot study of intravenous ibandronate has demonstrated palliation of opioid-resistant pain in a small number of patients with metastatic bone disease.[78] Mean pain scores at baseline were 5 to 6 on a 10-point scale; pain scores at 7, 21, and 42 days after ibandronate treatment were less than 4 on the same scale ($P<0.001$ for each time point). In addition, QOL improved by approximately 2 points on a 10-point Edmonton Symptom Assessment System scale, and improvements were maintained throughout the 42-day study ($P<0.05$ at each time point). Data from one placebo-controlled, randomized trial showed that ibandronate reduced pain (pain score change –0.28 versus +0.21 on a 5-point scale; $P<0.001$) and improved QOL in patients with metastatic bone disease.[75,78] Small phase II trials that used high loading doses of ibandronate also reported rapid palliation of opioid-resistant pain and improvements in QOL; however, the safety and efficacy of such dosing regimens are yet to be confirmed.[75,78] Although results from breast cancer studies are encouraging, data from large, prospectively defined trials are necessary to determine the efficacy of ibandronate in patients with

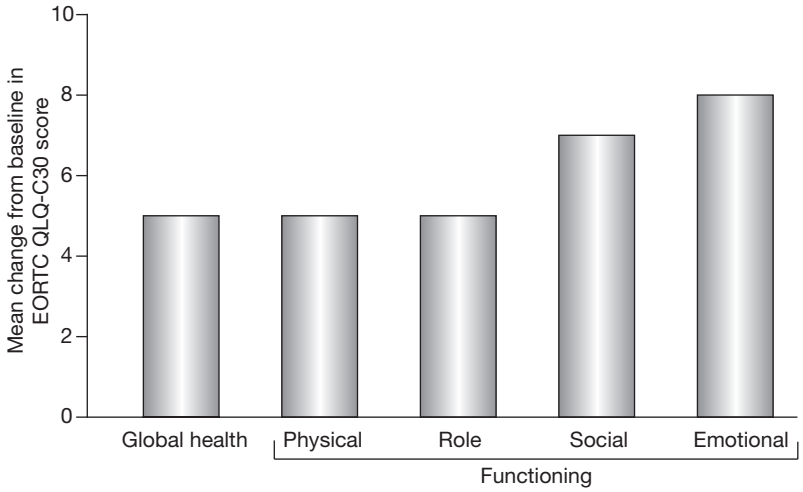


**Figure 2** Zoledronic acid improves quality of life measures in patients with bone metastases from breast cancer. Overall mean change from baseline reported at final visit (after nine infusions). Zoledronic acid exhibited significant improvements from baseline ($P<0.05$) in all domains except role functioning. Adapted with permission from Macmillan Publishers Ltd © Wardley A *et al.* (2005) *Br J Cancer* **92:** 1869–1876.[89] Abbreviation: EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Core Questionnaire 30.

bone metastases from solid tumors other than breast cancer.

Zoledronic acid is the newest nitrogen-containing bisphosphonate and is the only agent that has demonstrated efficacy in patients with hormone-refractory prostate cancer, breast cancer, multiple myeloma, or lung cancer and other solid tumors. The use of zoledronic acid is of particular interest given the ability of bisphosphonates to reduce pain by treating the underlying source of the problem. Zoledronic acid has demonstrated effectiveness in the prevention and delay of SREs in patients with multiple myeloma or bone metastases from a variety of tumor types in the clinical setting (Table 3 [an enlarged version of Table 3 that includes information on additional studies is available online]).[23,24,81–95] Its use for palliation of bone metastases has been studied in breast cancer in a randomized, placebo-controlled trial, in which this agent provided consistent and durable reductions in pain[82] and improvements in QOL (Figure 2).[89] Moreover, zoledronic acid (4 mg) produced an approximate 40% drop in the risk of developing an SRE for patients with breast cancer ($P=0.019$) compared with placebo.[82] Zoledronic acid consistently reduced Brief Pain Inventory composite pain scores from baseline compared with placebo throughout this study (Figure 3).[82]

Zoledronic acid has also been compared with pamidronate in patients with breast cancer or multiple myeloma and at least one bone lesion.[87] In this noninferiority trial, patients were randomly allocated to receive either zoledronic acid or pamidronate every 3–4 weeks. This trial was not designed to assess the superiority of zoledronic acid in pain management, and no significant differences in pain scores were observed between treatment groups. Treatment with 4 mg zoledronic acid, however, significantly decreased the proportion of patients who required palliative radiotherapy to the bone, which is a surrogate marker for bone pain, compared with 90 mg pamidronate during the first 13 months of the study ($P=0.018$).[87] In a subanalysis of the breast-cancer cohort, the time to first SRE was 136 days longer in the 4 mg zoledronic acid group than in the pamidronate group ($P=0.013$).[88] Andersen-Gill multiple event analysis showed that the risk of developing an SRE was also 20% lower for all patients with breast cancer treated with zoledronic acid compared with those treated with pamidronate ($P=0.037$).[88] In the 24-month extension of the original study, 4 mg zoledronic acid reduced the overall risk of developing a skeletal complication (including hypercalcemia of malignancy) by 16%, compared with pamidronate ($P=0.030$).[23] Consistent with the 13-month results, no differences in pain scores for each treatment group were observed; however, significant differences were evident in the proportions of patients who required palliative radiotherapy to the bone (19% for the 4 mg zoledronic acid group versus 24% for the pamidronate group; $P=0.037$).[23] Moreover, when adjusted for survival, 4 mg zoledronic acid was associated with a significantly reduced cumulative mean number of administrations of radiation to the bone—by 35.4%—compared with pamidronate at 25 months, and this reduction was consistent throughout the course of the trial ($P=0.003$).[96] The importance of this study was its use of an active-treatment control group. Not only did zoledronic acid show benefit, but it demonstrated significant superiority to the well-studied, early-generation, nitrogen-containing bisphosphonate pamidronate in the subset analyses of patients with breast cancer ($P=0.046$). This active-control trial was designed to establish noninferiority of zoledronic acid to pamidronate, and hence the study was not powered to detect differences in pain control between treatments.

The effectiveness of zoledronic acid in patients with hormone-refractory prostate cancer has also been shown in a large, multicenter, placebo-controlled trial. In the original analysis of data from

this trial, patients treated with 4 mg zoledronic acid had an 11% lower absolute incidence of SREs than patients treated with placebo (44.2% versus 33.2%, $P=0.021$) during a 15-month period.[83] The study was extended to 24 months and zoledronic acid (4 mg) significantly reduced the proportion of patients who had at least one SRE by 11% relative to placebo (38% versus 49%, $P=0.028$). The annual incidence of SREs was 0.77 for the zoledronic acid group versus 1.47 for the placebo group ($P=0.005$).[24] Compared with placebo, 4 mg zoledronic acid reduced the ongoing risk of SREs by 36% ($P=0.002$).[24] Mean pain scores were also significantly lower in patients who received zoledronic acid compared with placebo-treated individuals at the first (3 months, $P=0.003$)[97] and final (24 months, $P=0.024$) study assessments.[24] Zoledronic acid is the only bisphosphonate with broad regulatory approval for use in patients with bone metastases from prostate cancer.

A significant decrease in bone pain compared with baseline for patients with bone metastases from multiple cancer types was also reported in another large, open-label, single-arm study.[81] This study, conducted in community centers, assessed the safety of zoledronic acid for approximately 6 months in patients with multiple myeloma, breast cancer, or prostate cancer with and without previous bisphosphonate exposure. In the 638 patients studied, pain scores decreased significantly from baseline ($P<0.05$) and QOL scores remained constant.[81]

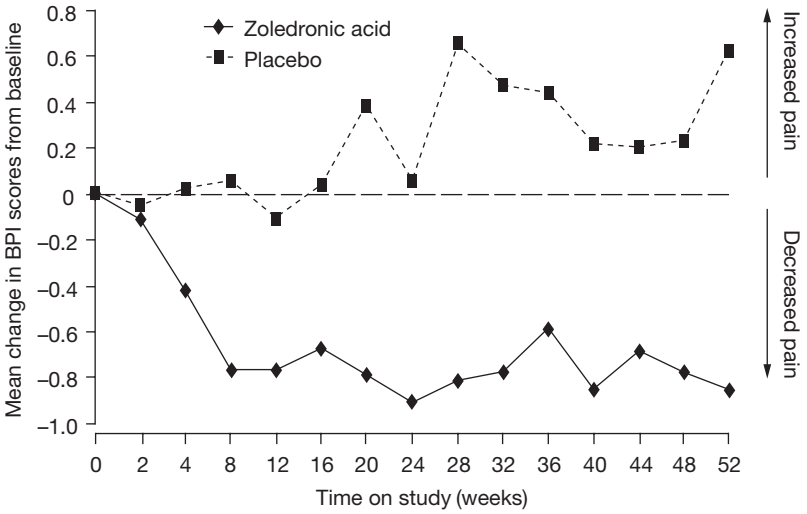


**Figure 3** Mean change from baseline in Brief Pain Inventory composite pain scores by treatment group and time on study. Patients continued to receive chemotherapy or standard treatment for breast cancer. Decreases in pain scores associated with zoledronic acid were statistically significant ($P<0.05$) versus placebo at all time points from 4 weeks onwards. Reprinted with permission from the American Society of Clinical Oncology © Kohno N *et al.* (2005) Zoledronic acid significantly reduces skeletal complications compared with placebo in Japanese women with bone metastases from breast cancer: a randomized, placebo-controlled trial. *J Clin Oncol* **23:** 3314–3321.[82]

## CONCLUSIONS

Bone pain and SREs in patients with metastatic cancers result in the loss of functional independence and a decrease in patients' QOL. The underlying mechanisms of osteolysis weaken bone integrity and result in additional bone pain. Patients who suffer from bone metastases can require radiation treatment coupled with analgesic therapy or bone surgery. Although they reduce total bone pain, these treatments can cause pain flashes and fail to manage the underlying disease and source of the pain.

Bisphosphonates show promise in the prevention of SREs and for the palliation of bone pain. Their mechanism of action enables these agents to stop bone resorption, which strengthens bone and provides an overall improvement in the underlying basis for bone pain in patients with metastatic cancer. Different classes of bisphosphonates have different abilities to protect against SREs; nitrogen-containing bisphosphonates have considerably higher efficacy in this regard than the early-generation agents such as clodronate. Furthermore, although most bisphosphonates demonstrate an analgesic effect to some degree in patients with bone metastases zoledronic acid is the only therapy that has demonstrated effectiveness in the prevention, reduction, and delay of SREs in multiple tumor types. In addition, data have demonstrated that zoledronic acid can provide increased benefits for patients when administered before the onset of bone pain in multiple tumor types.[98] Moreover, treatment continues to provide benefits to patients for up to 2 years of therapy, even after the onset of SREs.[99–102]

Zoledronic acid is also the only bisphosphonate to demonstrate superiority to pamidronate for some relevant end points; this result was obtained by direct comparison in a clinical trial that involved patients with breast cancer.[88] Zoledronic acid has also demonstrated efficacy in the long-term treatment of pain in patients with breast cancer or prostate cancer. The possibility of using zoledronic acid to not only control bone pain but also to prevent future SREs makes it an ideal candidate for use in the care of patients with bone metastases.

**Supplementary information** in the form of enlarged versions of Tables 2 and 3 is available on the *Nature Clinical Practice Oncology* website.

## KEY POINTS

- Bone metastases disrupt skeletal metabolism, which can result in disabling and potentially life-limiting skeletal-related events including pathologic fracture, spinal-cord compression, the requirement for surgery or radiation therapy to bone, and hypercalcemia of malignancy
- Bone metastases are the most frequent source of severe pain in patients with advanced cancers
- Skeletal-related events can reduce the functional independence of patients and undermine their quality of life
- Through the inhibition of bone resorption, bisphosphonates have demonstrated efficacy in delaying the onset and reducing the risk of skeletal-related events, as well as palliating bone pain
- Zoledronic acid is the only bisphosphonate that has demonstrated efficacy in reducing the risk of skeletal-related events in multiple cancer types, and in the long-term palliation of bone pain in patients with breast or prostate cancer

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**Competing interests**

L Costa has declared associations with the following companies: Amgen, Novartis and Roche. PP Major has declared associations with the following companies: Amgen and Novartis. See the article online for full details of the relationships.

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