EXPERT REVIEWS

Clinical efficacy and safety of zoledronic acid in prostate and breast cancer

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The anti-estrogen treatment for hormone-sensitive breast cancer and the androgen deprivation therapy for prostate cancer can lead to the development of osteoporosis and bone fractures. Metastases associated with prostate and breast cancer can also occur in bone. Bisphosphonates are used in these types of bone dysfunction. Zoledronic acid is the most potent bisphosphonate. In osteoporosis, zoledronic acid inhibits bone reabsorption and increases bone mineral density for at least a year after intravenous administration. The efficacy and safety of zoledronic acid in osteoporosis secondary to hormone-sensitive cancers (prostate and breast), and in the bone metastases associated with these cancers are reviewed.

Keywords: bisphosphonates • bone metastases • breast cancer • clinical trials • efficacy • osteoporosis • prostate cancer • zoledronic acid

Low levels of estrogens or testosterone are risk factors for primary osteoporosis. Osteoporosis can also be secondary to anti-estrogen treatment for hormone-sensitive breast cancer and to androgen deprivation therapy for prostate cancer. The metastases associated with breast and prostate cancer are often found in bone.

Bisphosphonates are commonly used to treat primary and secondary osteoporosis, and Paget's disease. The orally active bisphosphonates (e.g., alendronate) are used in the treatment of osteoporosis, with the more potent intravenous agents (e.g., zoledronic acid, pamidronate) often being preferred in secondary osteoporosis. The potent intravenous bisphosphonates are also used in the treatment of bone metastases associated with prostate and breast cancer. The bisphosphonates inhibit bone resorption, which is measured as a decrease in N-telopeptide and bone-specific alkaline phosphate, and an increase in bone mineral density. Molecularly, the bisphosphonates are enzyme-resistant analogs of pyrophosphate that bind to the bone minerals in the matrix and inhibit bone resorption by the osteoclasts.

Zoledronic acid (1-hydroxy-2-imidazol-1-yl-phosphonoethyl bisphosphoric acid) is a bisphosphonate used intravenously at intervals ranging from 3-times weekly to 6-times monthly (when it is used in cancer) to annually when it is used in osteoporosis. In bone metastasis, in addition to the zoledronic acid, patients are advised to take an oral calcium supplement of 500 mg and a multiple vitamin containing 400 IU of vitamin D [101].

A major advantage that intravenous zoledronic acid has over the oral bisphosphonates used in cancer is that it does not have gastrointestinal side effects, and this increases adherence. Thus, in 233 subjects with bone metastases, the persistence with intravenous zoledronic acid or pamidronate was 92%, which compared favorably to the 36% with oral bisphosphonates [1]. Zoledronic acid is more potent than other bisphosphonates, and this makes it suitable when the bone loss is pronounced.

This article reviews the efficacy and safety of zoledronic acid in the treatment of osteoporosis associated with prostate and breast cancer, and in the bone metastases associated with these cancers. The articles reviewed were obtained by searching PubMed for zoledronic acid and prostate cancer or breast cancer. Studies in which mixed cancers included prostate or breast cancer are not considered in the efficacy part of the review, but are considered in the section on safety. The use of zoledronic acid in prostate cancer is considered, and then the use of zoledronic acid in breast cancer. Serious adverse effects were not apparent in individual clinical trials when zoledronic acid was used to prevent fractures in subjects with primary osteoporosis [2,3] but have become apparent with long-term 3-times weekly

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to the 3-monthly use of zoledronic acid in cancer. These serious adverse effects with zoledronic acid are considered in a separate section. Finally, there is an expert commentary, which discusses the use of zoledronic acid in prostate and breast cancer.

Prostate cancer

Osteoporosis associated with hormone-sensitive prostate cancer

Bone loss in prostate cancer may occur prior to treatment and be due to the disease *per se*, and is also caused by orchiectomy or androgen deprivation therapy (e.g., gonadotrophin-releasing hormone [GnRH] agonists) for the cancer. When the GnRH agonists are used in the treatment of hormone-sensitive prostate cancer, it is probably the estrogen deficiency rather than low levels of testosterone that underlies the bone loss [4]. Both the androgen deprivation therapy and the bone metastases may contribute to the increased risk of fracture, pain and other skeletal complications in prostate cancer.

In hormone-sensitive prostate cancer being treated with androgen deprivation therapy, zoledronic acid has been shown to increase bone mineral density. Thus, when 106 men, without distant metastases from prostate cancer, began androgen deprivation therapy (a GnRH agonist with or without anti-androgen), were randomized to placebo or zoledronic acid (4 mg every 3 months for a year), the bone mineral density in the lumbar spine decreased by 2.2% in the placebo group, while increasing by 5.6% in the zoledronic acid group [5]. Bone mineral density was also increased in the femoral neck, trochanter and total hip of men treated with zoledronic acid. As men with prostate carcinoma often have low bone mineral density prior to hormonal treatment, increasing bone mineral density above the levels at the start of hormonal treatment may be considered to be a beneficial effect. There was no excess of adverse effects with zoledronic acid, compared with placebo. Since adverse effects on kidney function had been suggested when zoledronic acid was being used in primary osteoporosis, this was checked, and no detrimental effects of zoledronic acid on kidney function were noted [5]. In another study, where zoledronic acid (4 mg 3-times monthly for 1 year) was started 6–12 or over 12 months after the androgen deprivation therapy in 120 men with prostate cancer without bone metastases, zoledronic acid was also effective at increasing bone mineral density at the femoral neck, total hip and lumbar spine [6]. Adverse effects were similar in both groups and there was no renal dysfunction. As cases of osteonecrosis with zoledronic acid had been reported with the long-term use of zoledronic acid in other studies, this was determined, and there were no cases of osteonecrosis [6].

In androgen deprivation therapy for prostate cancer, it is desirable to prevent bone loss, but it may not be necessary to increase bone mineral density. As increasing the frequency of zoledronic acid doses seems to be associated with increased incidence of adverse effects, the smallest effective dose should probably be used. A study in 40 men with nonmetastatic prostate cancer, who had been treated with a GnRH agonist for over a year, was able to show a single intravenous injection of zoledronic acid 4 mg was sufficient to increase bone mineral density in the lumbar spine and total hip, while the density decreased in the untreated subjects after 12 months. Zoledronic acid was also shown to reduce serum bone alkaline phosphatase levels [7].

In men with prostate cancer being treated with androgen deprivation therapy, who also have bone metastases, the bone loss is likely to be caused by both the androgen deprivation therapy and the bone metastases. In a study lacking a placebo group, zoledronic acid (4 mg every 3 weeks for 1 year) was tested in 221 men receiving androgen deprivation therapy, who have prostate cancer with bone metastases, and was shown to increase bone mineral density at the lumbar spine by 7.7% and the total hip by 3.6%. influenza-like adverse effects were observed in some of the men. Thus, arthralgia (20.4%), nausea (14%), fatigue (14%) and back pain (12.2%) were the most common adverse effects with zoledronic acid in this uncontrolled study [8].

Bone metastases in hormone-refractory prostate cancer

Hormone-refractory prostate cancer occurs when hormone therapy fails to the stop the growth of prostate cancer. In prostate carcinoma, bone is a common, and sometimes the only, site for prostate cancer metastases, which occur in more than 80% of men with advanced prostate cancer.

A large study has shown that zoledronic acid 4 mg reduced clinical outcomes in bone metastases associated with prostate cancer. In this study, zoledronic acid 4 mg, or 8 mg reducing to 4 mg (8/4 mg), every 3 months for 15 months, were compared with placebo in 654 men with hormone-refractory metastatic prostate carcinoma, but only 31, 38 and 28% completed the trial in placebo, zoledronic acid 4-mg, and 8/4-mg groups, respectively [9]. The most common reasons for noncompletion were withdrawal of consent (31% with both regimens of zoledronic acid, 25% with placebo), adverse effects (28/29% with zoledronic acid, 21% with placebo) and death (22% with placebo, 19% with zoledronic acid 4 mg, 25% with zoledronic acid 8/4 mg). The primary efficacy variable was a skeletal-related event including pathological bone fractures, spinal cord compression, surgery to body, radiation therapy to bone and change in antineoplastic therapy to treat bone pain; this occurred less often with zoledronic acid 4 (33%) and 8/4 mg (39%) than with placebo treatment (44%) but was only significant for zoledronic acid 4 mg. Zoledronic acid 4 but not 8/4 mg, also prolonged significantly time to first skeletal-related event. There was a tendency, which was not significant, for zoledronic acid to reduce pain scores [9]. A subsequent different analysis of the pain data suggested that there was a significant, but small, increased chance of pain relief with zoledronic acid [10]. This suggested that any reduction of pain with zoledronic acid is small.

In this large study, zoledronic acid 8/4 but not 4 mg increased the risk of renal deterioration [9]. The other adverse effects were similar with the two regimens of zoledronic acid. Fatigue was a more common adverse effect with zoledronic acid 4 mg (32.7%) than with placebo (25.5%), as was anemia (26.6 vs 17.8%), myalgia (24.8 vs 17.8%), and lower limb edema (19.2 vs 13.0%) [9]. Overall, zoledronic acid 4 mg was more efficacious and less

detrimental than the 8/4-mg regimen in men with hormone-refractory metastatic prostate carcinoma [9]. The subjects who completed the 15-month study were reassessed at 24 months, with similar results for the comparison between zoledronic acid and placebo [11].

In another study, the effect of zoledronic acid on the pain associated with prostate cancer and bone metastases was studied in 18 subjects who had pain that was not controlled with analgesics [12]. In this uncontrolled study, pain decreased after treatment with zoledronic acid was started.

Breast cancer

Osteoporosis associated with hormone-sensitive breast cancer

In hormone-responsive breast cancer, the luteinizing-hormone-releasing analog goserelin or the aromatase inhibitors (e.g., anastrozole and letrozole) are used to reduce ovarian hormones and halt the cancer. However, as estrogens are required for the maintenance of bone mass in adult women, these endocrine treatments reduce bone mineral density and increase fracture risk (e.g., [13]).

In a study (Zometa-Femara Adjuvant Synergy Trial [Z-FAST]) of 301 postmenopausal women with estrogen- or progesterone-positive breast cancer being treated with letrozole, zoledronic acid (4 mg every 6 months) was started at the same time as letrozole or when the T score deteriorated to -2 [14]. Subjects were also receiving oral calcium supplement and vitamin D. In the delayed group, only 14% of subjects were receiving zoledronic acid by 12 months. Subjects administered zoledronic acid upfront showed small gains in bone mineral density in the lumbar spine and total hip after 6 or 12 months; whereas, with the delayed start there was a loss of bone mineral density and an increased risk of osteopenia. There was also greater decrease in the markers of bone turnover levels (N-telopeptide and bone-specific alkaline phosphatase) in the upfront compared with the delayed zoledronic acid treatment groups [14]. Similar results were obtained in the similar ZO-FAST study [15]. When the results of Z-FAST were combined with the ZO-FAST study, there were 1667 subjects and similar results were obtained for bone mineral density and bone markers; the fracture numbers were similar in both groups (~2%) after 12 months [16]. The Z-FAST study has been continued and, at 36 months, the bone mineral density remained higher in those women given zoledronic acid upfront than those in which zoledronic acid administration was delayed until the osteoporosis was apparent [17]. Thus, upfront zoledronic acid is more effective than delayed zoledronic acid in inhibiting the bone loss in postmenopausal women. The incidence of fractures was 5.7% in the upfront group and 6.3% in the delayed group, and these values were not significantly different. No severe renal dysfunction or confirmed cases of osteonecrosis of the jaw were observed. Disease recurrence was reported in 3.0% of upfront and 5.3% of delayed zoledronic acid subjects [17].

The Austrian Breast and Colorectal Cancer Study trial-12 (ABCSG-12) investigated whether zoledronic acid (4 mg/6 months) could prevent goserelin or goserelin/anastrozole bone loss in 404 premenopausal women with breast cancer [18]. After 3 years, bone mineral density in the lumbar spine had decreased by 14.4%, and the effect was greater with the goserelin/anastrozole combination (17.4%) than goserelin alone (11.6%) [18]. This bone loss was prevented by treatment with zoledronic acid. As usual, the first administration of zoledronic acid was associated with influenza-like symptoms (i.e., nausea, vomiting, fever and myalgia) but no changes in renal function. At this time, no fractures or other skeletal-related events had been observed [18]. All adjuvant treatment was then stopped, and the subjects were assessed after 2 years; those not treated with zoledronic acid still had reduced bone mineral density at the lumbar spine (6.3%), whereas those treated with zoledronic acid had an increased bone mineral density (4.0%) [19].

In a subsequent analysis, the anticancer activity of zoledronic acid in ABCSG-12 was assessed by comparing the risk of disease progression in the women treated with the endocrine treatment alone with that in those additionally treated with zoledronic acid [20]. This comparison showed that zoledronic acid caused an absolute reduction of 3.2% in the risk of disease progression over 3 years. In addition, subjects treated with zoledronic acid had locoregional and distance recurrence, bone metastases and disease in the contralateral breast. There were no confirmed cases of osteonecrosis of the jaw, and no serious renal events in ABCSG-12 [20].

Bone metastases in breast cancer

Bone metastases are commonly associated with advanced breast cancer, and zoledronic has been trialed in this situation. Thus, zoledronic acid (4 mg every 4 weeks for 1 year) has been compared with placebo in 228 Japanese women with bone metastases from breast cancers and shown to be efficacious [21]. On enrolment, the women had breast disease with at least one osteolytic bone metastasis and most were being treated with both hormonal therapy and chemotherapy (~40%), some with just hormonal therapy (~27%) and some with just chemotherapy (~26%). After 12 months, skeletal-related events (pathological fracture, spinal cord compression, radiation or surgery to bone) had occurred in 49.6% of those in the placebo group and this was reduced to 29.8% by zoledronic acid. Zoledronic also delayed the time to the first event and reduced the bone pain scores. Zoledronic acid increased the incidence of pyrexia, nausea and fatigue, while having no serious effects on kidney function [21]. In two other studies in women with breast cancer and metastases, zoledronic acid was shown to reduce pain scores and improve quality of life scores to a small extent, compared with baseline [22,23].

Prior to the development of zoledronic acid, pamidronate was the standard treatment for metastatic breast cancer and had been shown to reduce the number of skeletal-related events [24]. Zoledronic acid has been compared with pamidronate for bone metastases in breast cancer. A study of 1130 subjects with breast cancer with bone metastases, compared zoledronic acid and pamidronate and found that they had similar effects on skeletal-related events (pathologic fracture, spinal cord compression, radiotherapy or surgery to bone) [25]. Approximately half the subjects had osteolytic (rather than nonlytic) lesions and, in these subjects,

zoledronic acid 4 mg was more effective than pamidronate. Also, zoledronic acid prolonged the time to first skeletal event from 174 days with pamidronate to 310 days with zoledronic acid [25].

A small study has suggested that in subjects with breast cancer who have already had a skeletal-related event or have progressive bone metastases despite treatment with pamidronate or clodronate, a substitution with zoledronic acid may be beneficial. In this uncontrolled study, 31 subjects were given zoledronic acid 4 mg after treatment with pamidronate or clodronate was stopped and showed reduced bone reabsorption (measured by urinary N-teleopeptide) and improved pain control [26]. These findings need confirmation in a controlled trial.

Meta-analysis of the use of bisphosphonates for breast cancer (both metastatic and early) suggests that zoledronic acid 4 mg reduced the risk of developing a skeletal event by 41%, compared with 33% with pamidronate 90 mg [27].

Serious adverse effects

Overall, the tolerability of zoledronic acid is quite good. The most common adverse effects of zoledronic acid are influenza-like symptoms, which are experienced when zoledronic acid is first administered, and these have been considered previously. This section convers the more serious adverse effects associated with zoledronic acid. More frequent dosing with zoledronic acid is used in the treatment of bone loss with cancer than in osteoporosis, and the more frequent dosing is associated with a higher incidence of adverse effects.

When zoledronic acid is used in subjects with multiple myeloma or breast cancer, renal impairment occurs in 9–10% of subjects in thet clinical trial setting, and as many as 10–20% outside of clinical trials [28]. Another study of subjects predominantly with breast cancer (52%; lung cancer, 16%; prostate cancer, 13%) demonstrated renal toxicity in 21% [29]. It is now recommended that kidney function should be tested in subjects before the administration of zoledronic acid and the dose reduced if there is mild kidney insufficiency [28].

To avoid renal deterioration, the product label for zoledronic acid was updated to include a warning of the possibility of renal impairment, restrictions for subjects with renal impairment and a recommended dose of 4 mg intravenously every 3 or 4 weeks for bone metastases. Despite this, a review of medical records of 122 subjects with hormone-refractory prostate cancer with bone metastases showed renal impairment in a quarter of subjects, and that renal impairment increased with duration of zoledronic acid use [30].

Osteonecrosis of the jaw is associated with the use of zoledronic acid in the treatment of cancer. Meta-analysis showed that osteonecrosis occurs with the high doses of zoledronic acid used to treat bone loss associated with cancer but not with zoledronic acid use in primary osteoporosis [31]. In 2005 six cases of osteonecrosis of the jaw were reproted in subjects with breast cancer treated with zoledronic acid as the only bisphosphonate [32]. Six more cases of osteonecrosis of the jaw in breast cancer subjects treated with zoledronic acid were reported in 2006 [33]. In a larger population of subjects with cancer (38% with breast cancer; 14% with multiple myeloma), the incidence of osteonecrosis of the jaw was only 1.3% (22 out of 1706 subjects treated with zoledronic acid) [34]. In total, 13 subjects were followed to determine recovery from osteonecrosis of the jaw, and it was shown that the three of seven subjects with multiple myeloma recovered completely within a year, whereas there was no healing in the subjects with breast cancer [34].

Cases of osteonecrosis of the jaw in subjects with hormone-refractory prostate cancer treated with zoledronic acid started to appear in 2005 [35], and in 2007 it was estimated that the incidence was 3% (three out of 104) [36]. Another study of 52 subjects with prostate cancer, demonstrated an incidence of osteonecrosis of 12% with zoledronic acid 4 mg every 3 or 4 weeks, although the occurrence often did not occur until after the ninth treatment [37].

Recently, case reports of inflammatory disease of the eye with zoledronic acid have started to be published (e.g., myeloma [38], metastatic renal cell carcinoma [39] and breast cancer [40]). The incidence of this rare adverse effect has not been determined to date.

Expert commentary

Surrogate versus clinical end points

In many clinical trials with zoledronic acid in osteoporosis, the primary outcome is change in bone mineral density. It is assumed that an increase in bone mineral density (surrogate end point) will lead to a decrease in fractures (clinical end point). This has been tested in postmenopausal women with osteoporosis [2], as well as in men and women with osteoporosis after a hip fracture, and was shown to be the case [3]. In hormone-sensitive prostate and hormone-sensitive breast cancer without bone metastases, the trials have been too small or short to detect any changes in clinical outcomes with zoledronic acid and, consequently, we cannot be absolutely certain that the change in bone mineral density will be sufficient to improve clinical outcomes. Zoledronic acid has been shown to decrease skeletal-related events (e.g., pathological fracture, spinal cord compression, radiation to bone and bone surgery) and pain in men with bone metastases in hormone-refractory prostate cancer [9,10], as well as skeletal-related events when bone metastases occur in breast cancer. Ongoing analysis is needed to determine whether decreased fractures do eventuate with zoledronic acid treatment in hormone-sensitive cancers, prior to the development of metastases.

Pain and quality of life are important clinical outcomes in bone metastases. There are several studies suggesting that zoledronic acid reduces pain in bone metastases [41–43], but these are before and after treatment with zoledronic acid, and do not consider a placebo response. There is a need for better controlled trials of the effects of zoledronic acid on pain and quality of life outcomes in metastatic cancer.

Anticancer effects

It has been suggested that zoledronic acid may have anticancer effects in its own right [44,45]. Preclinical trials have suggested that zoledronic acid has some anticancer mechanisms as it inhibits farnesyl synthase, which is part of the mevalonate pathway that is involved in many cancers [44,45]. Zoledronic acid also decreases the levels of vascular endothelial growth factors to inhibit

angiogenesis, which is required for tumor growth [45]. In experimental breast cancer bone metastases, zoledronic acid reduced the tumor growth in the mouse [46]. Additionally, in the mouse model of breast cancer, doses of doxorubicin and zoledronic acid, which alone had no effect on tumor size, combined to decrease tumor size [47]. Zoledronic acid enhances the effects of docetaxel on growth of prostate cancer tumors in the bone environment in an animal model [48].

In a small clinical study where zoledronic acid was combined with doxetaxel for the treatment of subjects with metastatic, hormone-refractory prostate cancer, the results were better than expected, prompting the authors to suggest synergistic or additive effects of docetaxel–zoledronic acid on tumor cells [49]. As discussed previously, zoledronic acid has recently been shown to have anticancer activity in premenopausal women with breast cancer in ABCSG-12 [16].

The anticancer potential of zoledronic acid is presently being assessed in the Adjuvant Zoledronic Acid to Reduce Recurrence (AZURE) [102] and ANZAC [103] clinical trials. AZURE is evaluating the ability of zoledronic acid to reduce the risk of cancer recurrence in 3360 premenopausal and postmenopausal women with stage II/III breast cancer [102]. ANZAC is testing whether zoledronic acid has anticancer effects when used in woman with breast cancer prior to surgery [103].

Osteonecrosis of the jaw

With zoledronic acid, the incidence of osteonecrosis of the jaw increases with repeated use. In cancer subjects, two approaches have been shown to decrease the incidence of osteonecrosis of the jaw with zoledronic acid. First, the dose frequency can be reduced. In androgen deprivation therapy for prostate cancer, zoledronic acidhas been used 3-monthly [2] but it has been shown to increase bone mineral density after 12 months with annual dosing [7]. Thus, it may be possible to use annual dosing of zoledronic acid with androgen deprivation therapy in prostate cancer. A recent study in subjects with multiple myeloma has tested whether reducing the frequency of administration of zoledronic acid reduces the risk of osteonecrosis of the jaw [50]. In total, 51 of the patients received monthly zoledronic acid, while 55 were treated monthly during the first year, and then every 3 months [50]. The incidence of skeletal-related events was similar in both groups, but osteonecrosis of the jaw only occurred in one subject who was changed to the 3-monthly treatment, compared with six subjects who continued monthly treatment [50]. These findings need confirmation in larger and longer trials. A trial is presently being undertaken comparing monthly versus the 3-monthly zoledronic acid in subjects with breast cancer [104]. The results of these trials will determine whether the frequency of dosing of zoledronic acid can be reduced in these conditions.

The second approach to decreasing osteonecrosis of the jaw is undertaking a dental check with treatment prior to dosing with zoledronic acid [51,52]. Dental check-up with treatment has also been shown to reduce the incidence of osteonecrosis of the jaw in subjects predominantly with breast cancer [51]. Thus, the incidence of osteonecrosis of the jaw was 7.8% in 127 subjects treated with zoledronic acid, but reduced to 1.7% in 117 subjects who underwent dental visits prior to treatment with zoledronic acid [51]. This safety measure should become part of the routine use of zoledronic acid in subjects with cancer. It is now being recommended that, for oncology patients, a dental check-up and completion of required treatment undertaken before zoledronic acid treatment is started [53].

Recently, a preliminary report of an increased risk of osteonecrosis of the jaw when zoledronic acid is used in combination with antiangiogenic factors, compared with being used without these factors [54]. As zoledronic acid has antiangiogenic activity in its own right, this may represent an additive effect. This observation needs to be checked in a large cohort of subjects who are taking zoledronic acid with or without antiangiogenic factors.

Is zoledronic acid better than denosumab in cancer?

RANKL is an important mediator of bone destruction in metastatic cancer. Denosumab is a monoclonal antibody to RANKL. A Phase II study of denosumab, compared with intravenous bisphosphonate (predominantly zoledronic acid) in 255 subjects with breast cancer and bone metastases, suggested that denosumab had a similar ability to bisphosphonates to decrease bone turnover and skeletal-related events [55,56]. A double-blind study comparing denosumab with zoledronic acid in the treatment of bone metastases in men with hormone-refractory prostate cancer is ongoing and this has a primary outcome of time to first skeletal-related event [105]. Further comparisons of denosumab and zoledronic acid are required in cancer, including studying the effects on pain relief and quality of life.

Five-year view

Zoledronic acid has been shown to reduce skeletal events in subjects with primary osteoporosis. Zoledronic acid is now being used in osteoporosis associated with hormonal treatment of prostate and breast cancer, where it has been shown to prevent bone loss. Zoledronic acid is also being used to treat the bone metastases associated with prostate and breast cancer and has been shown to reduce the skeletal-related events in these conditions. Precautions need to be taken to prevent osteonecrosis of the jaw with long-term, frequent use of zoledronic acid. Probably the most exciting finding with zoledronic acid is that it may have anticancer activity. In the next 5 years, the anticancer activity of zoledronic in prostate and breast cancer is likely to be fully evaluated, and then zoledronic acid may be used both to prevent osteoporosis and for its anti-cancer activity. The anticancer activity of zoledronic acid also needs to be tested in all cancers with bone metastases to determine the extent of this activity.

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Key issues

- Zoledronic acid is a potent bisphosphonate administered intravenously to treat the secondary osteoporosis associated with hormonal deprivation treatments in prostate and breast cancer, and to treat the bone metastases that can occur with these cancers.
- Zoledronic acid reduced the bone mineral loss associated with the secondary osteoporosis in hormone-sensitive prostate and breast cancer. However, we do not know whether this translates into a decrease in skeletal events, and this needs to be determined.
- Zoledronic acid has been shown to decrease skeletal-related events in bone metastases in hormone-refractory prostate cancer and breast cancer, and should be used extensively in these conditions.
- One of the most interesting recent findings is that zoledronic acid has anticancer activity in premenopausal women with breast cancer. Ongoing trials are determining whether zoledronic acid has anticancer activity in premenopausal women with breast cancer and at a later stage of breast cancer. Zoledronic acid should be tested in hormone-sensitive prostate cancer and in the bone metastases associated with cancers other than prostate and breast, to determine whether it has anticancer activity in these situations.
- Dental precautions need to be used widely to prevent subjects with cancer developing osteonecrosis of the jaw when treated with zoledronic acid.
- Is zoledronic acid better than denosumab in cancer? This question should be answered by ongoing trials.

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