# Efficacy of Bisphosphonates and Other Bone-Targeted Agents in Metastatic Bone Disease From Solid Tumors Other Than Breast and Prostate Cancers

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Keywords

Bisphosphonates, zoledronic acid, bone-targeted therapies, metastatic bone disease

**Abstract:** Metastatic bone disease complicates the course of malignancy in a substantial proportion of patients with advanced cancer. Bisphosphonates are now widely used to improve skeleton-related outcomes of patients with metastatic cancer to the bone. Most studies evaluating the efficacy of bisphosphonates and other bone-targeted agents have been performed in patients with metastatic breast and prostate cancer. Only a few studies have evaluated the role of bisphosphonates in other tumor types involving the skeletal system. We present a review of the clinical literature focusing on the current and potential roles of bisphosphonates (particularly zoledronic acid) and newer bone-targeted therapies in patients with metastasis to bone arising from solid tumors other than breast and prostate cancer.

### Introduction

Bone is the most common site for metastases in cancer patients and has been intensively studied in breast and prostate cancers, largely because of the prevalence of these diseases and the particularly high rates of skeletal metastasis.<sup>1</sup> However, bone metastases are more common than often realized in a wide range of malignancies. For example, clinically and at the time of autopsy, 20–50% of patients with lung, thyroid, and kidney cancers have bone metastases (Table 1).<sup>2-9</sup>

The lung is the most common site of metastasis in renal cell carcinoma (RCC), but bone metastases occur in 20–35% of patients with advanced disease.<sup>4</sup> Similarly, while malignant melanoma is known to metastasize mostly to visceral organs, a recent study reported that 18% of patients with stage IV malignant melanoma had bone metastases.<sup>9</sup>

Increased bone resorption is the hallmark of metastatic bone disease (MBD) leading to skeletal-related events (SREs), which include bone pain requiring radiotherapy or surgery, pathological fracture, spinal cord compression, and hypercalcemia. Without treatment to reduce bone resorption, it is estimated that patients with bone metastases from advanced cancer will experience, on average, 2–4 SREs per year.<sup>10</sup>

Primary Site of Malignancy	Incidence of Skeletal Metastasis	Median Survival After Bone Metastasis (months)	
Lung	20% <sup>2</sup>	9.7 <sup>3</sup>	
Kidney	20-35%4,5	$12^{4}$	
Thyroid	47% <sup>6</sup>	29 (all types) <sup>7</sup> 46 (DTC) <sup>8</sup>	
Melanoma	18%9	39	
Breast	65–75% <sup>43</sup>	50 (sol) <sup>44</sup> 25 (mult) <sup>44</sup> 24–32 (BM first) <sup>45,46</sup>	
Prostate	90% <sup>27</sup>	4047	

 Table 1. Incidence of Skeletal Metastasis According to Tumor

 Type

BM first=bone metastases before other solid organ metastases; DTC=differentiated thyroid carcinoma; mult=multiple bone metastases; sol=solitary bone metastasis.

Bisphosphonates are a class of bone-targeting agents that primarily inhibit osteoclast function and therefore decrease bone resorption; other functions of bisphosphonates include anti-tumor effects.<sup>11</sup> Several bisphosphonates, which may be given orally or intravenously, have been developed for the treatment of bone loss and MBD. One of the most potent agents is the nitrogen-containing bisphosphonate zoledronic acid (ZA), which is now widely used as a standard of care in reducing the incidence of SREs in MBD.

This review highlights the clinical data underpinning the role of bisphosphonates, with special reference to ZA in the management of MBD from solid tumors other than breast and prostate. It also discusses a wider adoption of newer agents, such as denosumab (Xgeva, Amgen), and other bone-targeting drugs in development.

# Studies Assessing Clodronate and Ibandronate

Only a few trials have assessed bisphosphonates for the treatment of MBD from solid tumors other than breast and prostate cancers. An early trial investigated the relatively less potent bisphosphonate clodronate in 66 patients with poorly responsive tumors, such as non–small cell lung cancer (NSCLC), bladder cancer, gastrointestinal cancers, kidney cancer, melanoma, and metastatic carcinoma of unknown origin. Only 50 patients were followed for more than 2 months and were able to be adequately evaluated. At 3 months, clodronate did not significantly reduce the pain score, but analgesic consumption was considerably reduced.<sup>12</sup>

Ibandronate, the more potent nitrogen bisphosphonate, was investigated in a randomized placebo-controlled trial in 77 patients with bone metastases from colorectal cancer. Ibandronate significantly reduced the proportion of patients with SREs (39% vs 78%; P=.019), prolonged the time to first event by at least 6 months (median, >279 days vs 93 days; P=.009), and significantly reduced the skeletal morbidity rate (mean, 2.36 vs 3.14; P=.018).<sup>13</sup>

# Studies of Zoledronic Acid in Multiple Tumor Types

ZA is a highly potent nitrogen bisphosphonate that has been shown to be effective in the treatment of skeletal complications in 3 large registration trials. These studies included patients with bone metastases secondary to breast and prostate carcinomas.14,15 Also, in a randomized phase III trial, ZA was compared to placebo in 773 patients with bone metastases from solid tumors other than breast and prostate.<sup>16</sup> Patients had advanced-stage malignancies, with more than 20 tumor types represented. Among enrolled patients, 378 had NSCLC (50%), 74 patients (10%) had RCC, 58 patients (8%) had small cell lung carcinoma, 17 patients had carcinoma of the head and neck (2%), and 11 patients had thyroid carcinoma (1%). Unknown and other types of primary tumors accounted for approximately 7% and 23%, respectively, of the remaining diagnoses. Intravenous ZA (4 mg or 8 mg) was administered every 3 weeks for 9 months, with concomitant antineoplastic therapy. The 8-mg dose was reduced to 4 mg (8/4-mg group) for renal safety reasons. The primary efficacy analysis was the proportion of patients with at least 1 SRE. ZA reduced the proportion of patients with an SRE and increased the time to first SRE.

Overall, ZA was well tolerated, and the treatment duration was extended to 21 months. An updated publication in 2004 reported the results after the extension phase of treatment.<sup>17</sup> Efficacy conclusions were not drawn from the 8/4-mg dose group because of the heterogeneity of the dose. The report confirmed the efficacy of ZA (4 mg) in decreasing the proportion of SREs, the annual incidence of SREs, and time to development of first SRE. A multiple-event analysis was carried out to account for the absolute number of SREs and for the timing between them in order to provide a more sensitive assessment of the risk of skeletal complications between the 2 treatment groups. Using this multipleevent analysis, a hazard ratio (HR) of 0.693 indicated a 31% reduction in the risk of developing SREs in patients treated with ZA (Table 2).

There was also a trend toward a small decrease in Eastern Cooperative Group Performance Status (ECOG PS) scores at the end of the study for patients who received ZA 4 mg versus patients who received

Treatment Arm	ZA (4 mg)	ZA (8/4 mg)	Placebo
Number of patients	257	266	250
Proportion of SREs including HCM	39% (P=.039)	36% (P<.05)	46%
Median time to first SRE (days)	236 (P=.0009)	219 (0.017)	155
Risk of developing SRE (HR)	0.693 (P=.003) (31% reduction)	0.676 (P=.003) (33% reduction)	1
Annual incidence of SREs	1.74 ( <i>P</i> =.012)	1.56 ( <i>P</i> =.001)	2.71
Best bone lesion response (All PRs)	21 (8%) (P=NS)	28 (11%) (P=NS)	11 (4%)
25% quartile time to first fracture (days)	294 (0.020)	NR	161
Median TTP of bone lesions (days)	145 (P=NR)	238 (P=NR)	109
Median TTP of disease (days)	89 (P=.089)	91 ( <i>P</i> =.007)	84
Median overall survival (days)	202.5 ( <i>P</i> =.929)	189 ( <i>P</i> =.445)	183

**Table 2.** Summary of Results of Long-Term Efficacy of Zoledronic Acid in Patients With Bone Metastases Secondary to Solid Tumors Other Than Breast and Prostate Carcinomas<sup>12</sup>

HCM=hypercalcemia of malignancy; HR=hazard ratio; NR=not reported; NS=non-significant; PR=partial response; SREs=skeletal-related events; TTP=time to progression; ZA=zoledronic acid.

placebo (with a lower number denoting better performance status). At 21 months, the mean increase in ECOG PS was 0.99 +/- 1.20 for the ZA 4 mg group and  $1.20 \pm - 1.22$  for the placebo group (P=.080). Biochemical markers of bone resorption tended to remain stable or increase slightly from baseline in patients treated with placebo. However, in patients treated with 4 mg of ZA, urinary levels of N-telopeptide and deoxypyridinoline decreased significantly from baseline. Longterm administration of ZA at a dose of 4 mg was found to be safe and well tolerated. The percentage of patients with increased serum creatinine was 10.9% for the 4-mg dose and 12.7% for the 8/4-mg group, versus 6.7% with placebo. Adjusting the treatment dose of ZA from 8 mg to 4 mg and the infusion time from 5 minutes to 15 minutes reduced grade 3 or 4 serum creatinine increases to 1.8% for the 4-mg dose, 1.1% for the 8/4-mg dose, and 1.8% for the placebo group.

Unlike earlier bisphosphonate trials, where there was no benefit demonstrated in solid tumors other than breast and prostate, this large, positive, registration trial led to ZA being licensed to prevent SREs in this patient population, and has become the standard of care in many countries.

# Studies of Zoledronic Acid in Individual Solid Tumor Types

Few trials have investigated ZA in patients with 1 particular solid tumor. However, a retrospective subset analysis of patients with RCC who were enrolled in the above ZA registration study was performed, and results were published separately.<sup>18</sup> In this subset of 74 patients, ZA (4 mg) was found to significantly reduce the proportion of patients with an SRE (37% vs 74% for placebo; P=.015). Similarly, ZA significantly reduced the mean skeletal morbidity rate (2.68 vs 3.38 for placebo; P=.014), extended the time to the first event (median not reached vs 72 days for placebo; P=.006), and extended time to first pathological fracture (median not reached vs 168 days for placebo; P=.003). A multiple-event analysis demonstrated that the risk of developing an SRE was reduced by 61% compared with placebo (HR, 0.394; P=.008). The median time to progression of bone lesions was significantly longer for patients who were treated with ZA (P=.014). The median overall survival showed a trend favoring ZA (295 days for ZA vs 216 days for placebo), but did not achieve statistical significance (P=.179).

The efficacy of ZA was investigated in a small, prospective, randomized, placebo-controlled trial that involved patients with bone metastases from urinary bladder cancer who were receiving palliative radiotherapy.<sup>19</sup> Forty patients were randomized to placebo or ZA for 6 months. Patients receiving ZA had a lower mean incidence of SREs (2.05 +/- 1.0 vs 0.95 +/- 0.9, respectively), and fewer patients experienced an on-study SRE (2 vs 8 patients, respectively). ZA also prolonged the median time to first SRE compared with placebo (16 weeks vs 8 weeks, respectively). Multiple-event analysis of SREs revealed that ZA decreased the risk of SRE development by 59% (HR, 0.413). ZA also increased the 1-year survival rate compared with placebo (36.3 +/- 11.2 vs 0%, respectively).

In a retrospective study of 803 patients with renal cancer who were treated at a single center, 32% (N=254) presented with or later developed bone metastases, and 83%

of these patients also developed metastases elsewhere.<sup>20</sup> The mean number of SREs experienced by the bone metastatic patients was 2.4; only 37 patients experienced no SREs. The skeletal morbidity rate (number of SREs per patient-years at risk) for patients who received or did not receive bisphosphonates was 1.0 and 1.4, respectively.

In a study of 144 patients with bone metastases from lung cancer (non-randomized), 87 patients experienced bone pain and received ZA 4 mg, and 57 patients received no ZA.<sup>21</sup> All patients received the same chemotherapy (docetaxel and carboplatin). Patients who received ZA had a statistically significant longer survival (P<.01). A statistically significant positive correlation was found between the number of cycles of therapy with ZA and overall survival (P<.01, Pearson correlation), as well as time to tumor progression (P<.01). These findings suggest that ZA may have an anti-tumor effect.

In another study of 150 patients with stage III and IV lung cancer who were receiving chemotherapy, patients were randomized 2:1 to receive monthly ZA (maximum, 12 months) or no ZA. However, treatment with ZA failed to demonstrate an advantage in progression-free survival or overall survival.<sup>22</sup>

# Comparison of Zoledronic Acid With Other Bisphosphonates

In breast cancer patients with at least 1 osteolytic lesion, ZA has shown superiority to pamidronate in delaying time to first SRE.<sup>23</sup> However, such comparisons are less well-documented in patients with solid tumors other than breast or prostate. In a Chinese study, 228 patients with bone pain induced by MBD from solid tumors and multiple myeloma were randomized to receive ZA or pamidronate. Both treatments reduced pain and bone resorption markers and were comparable in efficacy and tolerability.<sup>24</sup>

Another study compared the pain-relieving efficacy of ZA with ibandronate and pamidronate. Of the 280 patients accrued in the study, 187 were eligible for final analysis. Forty-five of these patients had breast or prostate cancer, 78 patients had lung cancer, 22 patients had gastrointestinal malignancy, 21 patients had bone and soft tissue cancer, and 21 patients had other primary malignancies. Patients were randomized to receive ZA, pamidronate, or ibandronate. There was no difference in pain scores among the 3 treatment arms assessed at 3 months. However, the pain scores at 6 months were significantly reduced in the ZA arm as compared to the other 2 arms. Also, the rate of hypercalcemia was significantly reduced among patients treated with ZA (28.3%) compared to patients who received ibandronate (44.6%) and pamidronate (50%) treatment (P=.041).25

# Comparison of Zoledronic Acid With Denosumab

Denosumab is a fully humanized monoclonal antibody that binds to the receptor activator of nuclear factor kappa-B ligand (RANKL), inhibiting osteoclast activity in the bone, which results in decreased bone resorption. A recent study compared denosumab with ZA in terms of delaying or preventing SREs in patients with advanced cancer (excluding breast and prostate cancers) and bone metastases.<sup>26</sup> Of note, this study included patients with multiple myeloma (180 out of 1,776 patients). The results of this study showed non-inferiority of denosumab to ZA in delaying time to first SRE as its primary endpoint. There was no difference in overall survival or disease progression between the 2 arms. However, a subgroup analysis of the largest group showed a survival advantage in the denosumab arm among the lung cancer group (including NSCLC). Future studies powered to further investigate this potential benefit are currently planned.

The adverse effect profiles of the 2 agents were similar, though with lower (non-significant) incidence of renal adverse events and no acute-phase reaction in the denosumab arm. Another advantage of denosumab is that it is administered subcutaneously rather than by intravenous infusion, as is the case for ZA.

# The Use of Bone Markers in Metastatic Bone Disease

Many biomarkers of the pathways occurring in bone metabolism have now been described, including those which have special relevance to metastatic bone disease. A detailed account of such bone markers is beyond the scope of this article, and there are already more detailed reviews on this topic.<sup>27,28</sup> However, the use of bone markers in monitoring the effects of bisphosphonates and other bone-targeted therapies is worthy of mention.

An analysis of bone markers measured prospectively in the placebo arm of a registration trial for ZA examining patients with NSCLC and other solid tumors showed that high levels of the bone resorption marker N-telopeptide of type I collagen (NTX) were a strong prognostic indicator of negative outcomes.<sup>29</sup> For patients with NSCLC and solid tumors other than breast and prostate, those with high N-telopeptide levels had an increased relative risk (RR) of SREs (RR, 1.79; 95% CI, 1.15–2.79; *P*=.010), disease progression (RR, 1.91; 95% CI, 1.16–3.15; *P*=.011), and death (RR, 2.67; 95% CI, 1.85–3.85; *P*<.001) compared with patients with low N-telopeptide levels. Corresponding analyses in the ZA arm of this trial showed that, when compared with low NTX levels, high NTX levels were associated with a fourfold to sixfold increase in the risk of death on study, and moderate NTX levels were associated with a twofold to fourfold increase in the risk of death on study (P<.001).<sup>30</sup>

In further analyses of all 3 ZA registration trials, normalization of NTX after 3 months of bisphosphonate treatment was associated with improvement in overall survival. Among the 291 patients with NSCLC and solid tumors other than breast and prostate who were treated with ZA, results showed that in patients with abnormal elevated baseline pretreatment levels of NTX, normalization of NTX occurred in 81% of patients treated with ZA and in 17% of patients treated with placebo. Risk of death was reduced in patients who were treated with ZA and had normalized NTX (RR of death, 0.43; 95% CI, 0.22–0.83; P=.0116) versus patients whose NTX remained elevated.<sup>31</sup>

A further illustration of the value of bone markers in trials of MBD is demonstrated by a phase II study of denosumab versus ZA (N=111), which included patients with solid tumors other than breast and prostate (n=15), who had elevated NTX despite ongoing bisphosphonate therapy.<sup>32</sup> Bone resorption was further suppressed in a higher percentage of patients who were treated with denosumab compared with those treated with ZA, as demonstrated by the number of patients with urinary NTX levels less than 50 nM (64% vs 37%, respectively) at week 13 of the study.

### **New and Emerging Bone-Targeted Therapies**

In recent years, a greater understanding of the biology of the bone metastatic process has led to a number of promising targets for novel agents. Elucidation of the RANK/RANK-L/osteoprotegerin axis led directly to denosumab, and other agents that target molecules in the bone metastasis pathway are in development. These include Src kinase inhibitors (such as dasatinib [Sprycel, Bristol-Myers Squibb], saracatinib, bosutinib [Bosulif, Pfizer], and cathepsin K inhibitors.<sup>33,34</sup> Alpharadin  $(^{223}\text{RaCl}_{2})$ , an  $\alpha$ -particle–emitting agent that localizes in bone, is very promising and has shown a survival benefit in a phase III study of patients with castration-resistant prostate cancer.<sup>35</sup> An especially interesting recent development concerns the potential use of skeletal anabolic agents. Sclerostin is a protein that is a potent inhibitor of osteoblastogenesis. Monoclonal antibodies to sclerostin, while still in the early stages of development, present new opportunities and may be especially valuable in diseases such as renal cancer, where the lesions are predominantly lytic.36 As expected, the first groups to be assessed with such new agents are patients with breast and prostate cancer. However, there is every reason to believe that these treatments could be utilized in other solid tumors.

### Survival and Possible Anti-Tumor Effect of Zoledronic Acid and Denosumab

Intriguingly, there is growing evidence suggesting that ZA improves progression-free survival and overall survival in patients with advanced cancer,<sup>13-15</sup> possibly due to direct and indirect anti-tumor effects.<sup>11,37</sup>

Large adjuvant trials with ZA are ongoing or have recently been completed. The 3,360-patient AZURE (Adjuvant Zoledronic Acid to Reduce Recurrence) study in breast cancer<sup>38</sup> compared adjuvant ZA given for 5 years with no adjuvant therapy. At a median follow-up of 59 months, there was no difference between groups in the primary endpoint, with a disease-free survival rate of 77% in each group (adjusted HR in the ZA group, 0.98; 95% CI, 0.85-1.13; P=.79). However, among postmenopausal patients, the rates of invasive-diseasefree survival were 78.2% in the ZA group and 71.0% in the control group (adjusted HR with ZA, 0.75; 95% CI, 0.59–0.96; P=.02) In addition, among patients who had undergone menopause more than 5 years earlier, the 5-year overall survival rate was 84.6% in the ZA group and 78.7% in the control group (adjusted HR, 0.74; 95% CI, 0.55–0.98; P=.04).

In a randomized, placebo-controlled trial of 1,432 men with castration-resistant prostate cancer and no bone metastases, denosumab significantly increased bone-metastasis–free survival by a median of 4.2 months compared with placebo (median, 29.5 months vs 25.2 months; HR, 0.85; 95% CI, 0.73–0.98; P=.028). Denosumab also significantly delayed time to first bone metastasis (33.2 months vs 29.5 months; HR, 0.84; 95% CI, 0.71–0.98; P=.032). However, overall survival did not differ between the 2 groups.<sup>39</sup>

Further studies of adjuvant use of bisphosphonates are being conducted in patients with breast, prostate, and lung cancer. Because of a subgroup analysis<sup>40</sup> of the phase III denosumab study<sup>33</sup> (mentioned earlier) showing a survival advantage for denosumab over ZA in lung cancer patients, a study is planned to look at this patient subgroup in more detail. However, no data are currently available regarding the efficacy of bisphosphonates or other bone-targeted therapies in the adjuvant setting for other solid tumors.

### Safety and Toxicity of Bone-Targeted Agents

Bisphosphonates have been administered for many years, both in the postmenopausal osteoporosis setting and in the MBD setting. During this time, the potency of the bisphosphonates commonly used has progressively increased, culminating in the nitrogencontaining bisphosphonates, ZA and ibandronate. The

higher and more intensive dosing regimens used in treating MBD as compared with osteoporosis can result in significant toxicity and side effects. For example, intravenous bisphosphonates such as ZA are associated with an acute, flu-like reaction on first use, and may have adverse effects on renal function, sometimes necessitating dose reduction.<sup>41</sup> Although relatively rare, the most serious associated toxicity is osteonecrosis of the jaw (ONJ). This is a severe condition that is strongly linked to poor dental health, especially that leading to tooth extraction.<sup>42</sup> ONJ is also associated with denosumab treatment, at approximately the same incidence as with ZA. The incidence and management of ONJ has become much more understood in recent years, and preventative measures, such as avoidance of tooth extraction and good dental health, are now emphasized. In recent trials, the cumulative incidence of ONJ has been approximately 1-2% per year.42

#### Conclusion

Relatively fewer clinical trial data are available regarding the use of bisphosphonates and other bone-targeted agents in patients with metastatic bone disease from primary tumors other than breast and prostate cancer. The available studies strongly suggest a benefit with bisphosphonates, particularly ZA, in terms of improvement in symptoms and a decrease in SREs. Denosumab has been shown to have a similar efficacy to ZA in this patient population, but has a relatively convenient mode of administration (subcutaneous) and is not associated with renal toxicity. However, despite these advances, SREs still occur. There is clear evidence for the use of ZA and denosumab in patients with bone metastases arising from solid tumors other than breast and prostate, and it is important to consider treatment with a bone-targeted therapy in such patients. There is reason to be optimistic that agents currently in development, either alone or in combinations with currently licensed bone-targeted therapy, will further improve prospects for these patients.

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