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Toward New Horizons:
The Future of Bisphosphonate Therapy

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Key Words. Adjuvant therapy · Bisphosphonates · Cancer-treatment-induced bone loss · Clodronate · Prostate cancer · Zoledronic acid

ABSTRACT
Bisphosphonate therapy has become a standard of care for patients with malignant bone disease. In addition, preclinical and preliminary clinical data suggest that bisphosphonates may prevent cancer-treatment-induced bone loss (CTIBL) and the development of malignant bone disease in patients with early-stage cancer. Patients who receive adjuvant hormonal therapy for breast cancer or androgen-deprivation therapy for prostate cancer are at an especially high risk for CTIBL because of reduced estrogenic signaling. Oral clodronate (Bonefos®; Anthra Pharmaceuticals; Princeton, NJ), oral risedronate (Actonel®; Proctor and Gamble Pharmaceuticals, Inc.; Cincinnati, OH), and i.v. zoledronic acid (Zometa®; Novartis Pharmaceuticals Corp.) and i.v. zoledronic acid both have demonstrated significant benefits over placebo, but only zoledronic acid produced significant increases in bone mineral density compared with baseline values. Additionally, bisphosphonates have demonstrated antitumor activities in preclinical models, and clinical trials with oral clodronate suggest that bisphosphonates might prevent or delay bone metastasis in patients with early-stage breast cancer. Clinical trials are investigating the effect of zoledronic acid on disease progression in patients with breast cancer, prostate cancer, and non-small cell lung cancer. The results of these clinical trials should further define the clinical benefit of bisphosphonates in the oncology setting. The Oncologist 2004;9(suppl 4):38-47

LEARNING OBJECTIVES
After completing this course, the reader will be able to:

1. Discuss the role of bisphosphonates in managing bone disease in the setting of cancer and its treatment.
2. Describe differences in treatment paradigms for bone loss as a complication of cancer and its treatment versus benign bone loss.
3. Explain the mechanism of action of bisphosphonates in the setting of malignant bone disease.

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INTRODUCTION

Treatment innovations have provided promising improvements in survival for patients with cancer. However, cancer and its treatment can have profound effects on bone and are associated with an increased risk of fractures and other skeletal complications [1, 2]. Cancer-treatment-induced bone loss (CTIBL) and malignant bone disease can result in significant skeletal morbidity that can decrease quality of life and, potentially, survival [3]. For these reasons, preservation of skeletal health is emerging as an important aspect of patient care in the oncology setting, as reflected by the recent update of the American Society of Clinical Oncology guidelines for treating patients with breast cancer [4]. Patients who are receiving treatment for early-stage cancer are at risk for CTIBL, and patients with advanced cancer are at risk for bone destruction from bone metastases. Bisphosphonates have demonstrated significant clinical efficacy in preventing bone loss and the skeletal complications associated with bone metastases. Therefore, the role of bisphosphonate therapy in the oncology setting is expanding to fill the emerging need for maintaining bone health throughout the continuum of care in patients with cancer. Recent evidence suggests that bisphosphonates may also have direct antitumor effects at clinically achievable concentrations, suggesting that the future role of bisphosphonates may continue to expand [5].

Bisphosphonates are potent small-molecule inhibitors of osteoclast-mediated osteolysis and are an established treatment for benign osteoporosis and other disorders of bone metabolism such as Paget’s disease. In the setting of malignant bone disease, bisphosphonates delay and prevent skeletal complications, although more intense dosing is required than in the setting of benign bone loss. Intravenous bisphosphonate therapy has been the standard of care for patients with bone lesions from multiple myeloma or bone metastases secondary to breast cancer since the mid-1990s, and the recent introduction of zoledronic acid (Zometa®; Novartis Pharmaceuticals Corp.; East Hanover, NJ) has since extended the benefits of bisphosphonate therapy to patients with bone metastases secondary to prostate cancer, lung cancer, or other solid tumors. Preclinical and preliminary clinical results suggest that bisphosphonates, in general, and zoledronic acid, in particular, may provide additional benefits beyond their current applications. Clinical trials are currently investigating the efficacy of bisphosphonates to prevent CTIBL and the development of bone metastases in patients with breast cancer, prostate cancer, renal cell cancer, and lung cancer. The results of those trials will help to define the future clinical applications of bisphosphonates in the oncology setting.

PREVENTION OF CTIBL

Improvements in cancer screening and early detection have resulted in the earlier diagnosis of cancer, thus increasing the proportion of patients who receive treatment while they still have early-stage disease. Although successful therapy for early-stage cancer means that treated patients typically survive longer, they may develop complications from the long-term effects of therapy. Cytotoxic chemotherapy, hormonal therapy, and radiation therapy are all associated with bone loss in some patient populations [2]. Based on the numbers of affected patients, hormonal therapies resulting in estrogen or androgen depletion in breast cancer and prostate cancer are the main causes for CTIBL.

Hormonal agents that block estrogenic or androgenic signaling are widely used and highly effective therapies for breast and prostate cancer [6, 7], which are the most common noncutaneous malignancies in women and men, respectively [8]. However, these hormone signaling pathways also play important roles in maintaining skeletal homeostasis. Hormonal therapies can reduce the levels of estrogenic signaling below that seen in postmenopausal women (Fig. 1) [6, 9, 10]. Consequently, the rates of bone loss associated with cancer treatment appear to be more rapid than those observed in postmenopausal women (Table 1) [11-28]. For example, in women receiving adjuvant hormonal therapy with aromatase inhibitors (e.g., letrozole [Femara®; Novartis Pharmaceuticals Corp.] or anastrozole [Arimidex®; AstraZeneca Pharmaceuticals; Wilmington, DE]) or ovarian ablative therapies (e.g., oophorectomy or cyclophosphamide) for breast cancer, rates of bone loss are at least double those reported during early menopause, when natural bone loss is usually the most profound [11-16, 21]. The same is true for men receiving androgen-deprivation therapy (ADT) for prostate can-

![Figure 1. Bioavailable estradiol (E2) concentrations in patients at risk for bone loss. Adapted with permission from Khosla et al. [10]. Data from Smith et al. [66].](http://theoncologist.alphamedpress.org/Downloaded from)
cer [22, 29, 30], especially those who have recently received therapeutic orchiectomy, which appears to trigger an especially profound CTIBL that can result in loss of up to 9.6% of hip bone mineral density (BMD) in the first year [23]. Moreover, a recent study of biochemical markers of bone metabolism demonstrated that men who are receiving ADT for prostate cancer (early stage or metastatic) have significantly higher levels of the osteolytic marker N-telopeptide than men who have not received hormonal therapy ($p < 0.001$) [31]. That study provides support for the inference that increased levels of osteolysis cause bone loss in patients receiving ADT for prostate cancer.

As a result of CTIBL, patients are at a substantially increased risk for fractures. Increased fracture risks have been reported for patients receiving aromatase inhibitors for breast cancer [32] or ADT for prostate cancer [33, 34]. For example, in a recent long-term clinical trial of anastrozole and tamoxifen (Nolvadex®; AstraZeneca; Wayne, PA) in postmenopausal women with early-stage breast cancer, 7.1% of the patients treated with anastrozole and 4.4% of those treated with tamoxifen experienced fractures over 5 years. Similarly, a cross-sectional study of patients receiving long-term ADT for prostate cancer revealed that the overall relative risk of hip fracture was 20% higher in patients on ADT for 1-3 years and was 95% higher in patients on ADT for 5 years compared with rates in patients who had received radical prostatectomy but no ADT [35].

There is currently no therapy approved specifically for treating or preventing CTIBL; however, early evidence from clinical trials suggests that bisphosphonates may be effective for the treatment and prevention of CTIBL in patients with early-stage cancer [6, 7]. Although oral bisphosphonates are widely used for the treatment of benign osteoporosis, CTIBL appears to be more rapid and severe than benign osteoporotic conditions, so more potent therapy may be required. Intravenous bisphosphonates may be better tolerated and can be administered less frequently than oral bisphosphonates [36]. Zoledronic acid is a new generation bisphosphonate that has the shortest approved infusion time of all bisphosphonates, and it has demonstrated activity in the prevention of CTIBL when administered as infrequently as every 3 or 6 months [28, 37].

### Clinical Trials in Patients With Early-Stage Breast Cancer

In the early breast cancer setting, both oral and i.v. bisphosphonates have been investigated for the prevention of CTIBL. Daily oral clodronate (Bonefos®; Anthra Pharmaceuticals; Princeton, NJ) and intermittent oral risedronate (Actonel®; Proctor and Gamble Pharmaceuticals, Inc.; Cincinnati, OH) both have demonstrated activity. Daily oral clodronate (1,600 mg/day) resulted in significantly less bone loss than placebo in patients with breast cancer treated with antiestrogen therapy (tamoxifen and toremifene [Fareston®; Orion Corporation; Espoo, Finland]; $p = 0.001$ for lumbar spine and $p = 0.006$ for femoral neck) [38] and in patients with chemotherapy-induced ovarian dysfunction ($p = 0.0005$ for lumbar spine and $p = 0.017$ for femoral neck) [18]. However, in the latter group of patients, clodronate was unable to completely prevent bone loss, and patients with chemotherapy-induced amenorrhea experienced bone loss in the lumbar spine at a rate of approximately 3% per year despite clodronate treatment. In a 2-year clinical trial in women with breast cancer and chemotherapy-induced menopause, eight cycles of oral risedronate (30 mg/day for the first 2 weeks of each 12-week cycle) preserved greater BMD in the lumbar spine and femoral neck than placebo ($p = 0.041$ and $p = 0.029$, respectively; Fig 2) [19]. More recently, Gnant et al. [37] reported the preliminary results of an Austrian Breast and Colorectal Cancer Study Group trial (ABCSG-012; tar-
geted accrual, \( n = 1,250 \) of i.v. zoledronic acid in premenopausal women receiving goserelin plus anastrozole or tamoxifen. In the first 172 patients to complete 1 year of therapy, zoledronic acid (4 mg by 15-minute i.v. infusion every 6 months) significantly preserved BMD in the lumbar spine (L1 to L4) \( (p < 0.0001) \) and trochanter \( (p < 0.002) \) among patients treated with anastrozole (Fig. 3) [37]. Bone loss was more profound in patients treated with anastrozole than in those treated with tamoxifen \( (p = 0.0125) \) [37]. Zoledronic acid prevented bone loss associated with both treatment regimens.

In addition to the ABCSG-012 trial, which is still in progress, the parallel-design Zometa®/Femara® Adjuvant Synergy Trials (Z-FAST and ZO-FAST in the U.S. and Europe, respectively) are investigating the benefit of immediate and delayed treatment with zoledronic acid (4 mg every 6 months) in postmenopausal women receiving adjuvant therapy with letrozole (2.5 mg/day) for early-stage hormone-receptor-positive breast cancer. Those trials will also enroll women in whom menopause has been induced by chemotherapy. In the delayed therapy group, patients will receive zoledronic acid only if they experience an asymptomatic fracture by the 36-month time point or develop severe osteopenia or a clinical fracture at any point during the trial. The primary end point in these trials is change in lumbar spine BMD (L1 to L4 for Z-FAST; L2 to L4 for ZO-FAST). Other end points include changes in lumbar spine BMD at 2, 3, and 5 years, changes in hip BMD at 1, 2, 3, and 5 years, rate of change in lumbar spine and hip BMD, clinical fractures, biochemical markers of bone metabolism, safety, and disease-free survival. The Cancer and Leukemia Group B (CALGB) is also planning a trial (CALGB79809) to assess the efficacy of i.v. zoledronic acid (4 mg every 3 months) in premenopausal women with chemotherapy-induced ovarian failure. Zoledronic acid will be administered either immediately or after 1 year. The targeted accrual for CALGB79809 is 400, and the primary end points are lumbar spine BMD at 12 and 36 months.

Based on the results from early clinical trials, bisphosphonates appear to be effective for the prevention of CTIBL. Current consensus guidelines from the American Society of Clinical Oncology recommend the use of i.v. or oral bisphosphonate therapy in patients who develop T scores below -2.5 standard deviations from normal (osteoporosis) during adjuvant therapy for breast cancer [4]. The results from the ongoing clinical trials described above will provide insight into the optimal dosing schedule and the best time to initiate bisphosphonate therapy.

**Clinical Trials in Patients With Early Prostate Cancer**

Although alendronate (Fosamax®; Merck and Company, Inc.; West Point, PA) is the only bisphosphonate currently approved for the treatment of osteoporosis in men, this oral
therapy has not been tested in patients with prostate cancer [22]. In contrast, etidronate (Didronel®; Procter and Gamble Pharmaceuticals, Inc.), pamidronate (Aredia®; Novartis Pharmaceuticals Corp.), and zoledronic acid have all been shown to prevent bone loss in patients receiving ADT for prostate cancer (Table 2) [22, 27, 28, 39, 40].

In the first of these studies [39], 12 consecutive men were treated with etidronate (400 mg oral daily for 2 weeks q 3 months) 6 months after beginning continuous therapy with goserelin (Zoladex®; AstraZeneca) and flutamide (Schering-Plough Corporation; Kenilworth, NJ). At 1 year, cyclic etidronate therapy was shown to result in significantly greater lumbar spine and femoral neck BMDs relative to the 6-month values ($p < 0.001$ and $p = 0.001$, respectively), but BMD remained significantly lower than baseline ($p < 0.01$).

Subsequent studies investigating the potential of bisphosphonates to prevent CTIBL in men with prostate cancer have focused on more potent i.v. bisphosphonates. The first of these, a small crossover study ($n = 21$) of a single 90-mg infusion of pamidronate in men receiving goserelin and flutamide therapy for metastatic prostate cancer [40], suggested that pamidronate had significant activity. In a subsequent 48-week placebo-controlled study in men receiving leuprolide (Lupron Depot®; TAP Pharmaceuticals; Lake Forest, IL; Eligard®; Sanofi-Synthelabo Inc.; New York, NY) therapy for advanced or recurrent prostate cancer ($n = 47$), i.v. pamidronate (60 mg) was administered every 12 weeks [27]. Compared with the placebo group, patients treated with pamidronate had significantly higher BMDs in the lumbar spine ($p < 0.001$), trochanter ($p = 0.003$), and total hip ($p = 0.005$). However, pamidronate did not significantly

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**Table 2. Annual percent change in lumbar spine and hip BMD in men with prostate carcinoma receiving ADT in randomized controlled trials**

<table>
<thead>
<tr>
<th>Study</th>
<th>$n$ of patients</th>
<th>Treatment</th>
<th>Annual BMD change (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>LS DEXA</td>
</tr>
<tr>
<td>Diamond et al. [39]</td>
<td>12</td>
<td>CAB alone + etidronate (400 mg oral daily for 2</td>
<td>$-6.6$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>weeks q 3 months)</td>
<td></td>
</tr>
<tr>
<td>Smith et al. [27]</td>
<td>47</td>
<td>CAB alone</td>
<td>$-3.3$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>+ pamidronate (60 mg q 3 months)</td>
<td>$+0.5$</td>
</tr>
<tr>
<td>Diamond et al. [40]</td>
<td>21</td>
<td>CAB alone + pamidronate (90 mg single infusion)</td>
<td>$-5.7$</td>
</tr>
<tr>
<td>Smith et al. [28]</td>
<td>106</td>
<td>GnRH agonist alone (± antiandrogen)</td>
<td>$-2.2$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>+ zoledronic acid (4 mg q 3 months)</td>
<td>$+5.6$</td>
</tr>
</tbody>
</table>

**Abbreviations:** LS = lumbar spine; DEXA = dual-energy x-ray absorptiometry; QCT = quantitative computed tomography; CAB = combined androgen blockade; q = every; GnRH = gonadotropin-releasing hormone.

Adapted with permission from Diamond et al. [22]

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**Figure 4. Effect of i.v. bisphosphonate therapy on BMD during ADT.** The calculated change in BMD after 1 year of ADT in: A) men treated with pamidronate (gray bars) or no bisphosphonate (white bars) and B) men treated with zoledronic acid (black bars) or placebo (white bars). Adapted with permission from Smith et al. [27, 28].
increase BMD compared with baseline values (Fig. 4A) [27]. More recently, a larger, randomized, placebo-controlled trial investigated the benefit of zoledronic acid (4 mg by 15-minute infusion every 3 months for 1 year) in men receiving initial ADT with a gonadotropin-releasing hormone agonist for stage M0 prostate cancer. That study revealed that zoledronic acid not only prevented bone loss better than placebo ($p < 0.001$ for all sites; Fig. 4B) [28] but also significantly increased BMD by 5.6% in the lumbar spine ($p < 0.001$), 1.2% in the femoral neck ($p = 0.018$), 2.2% in the trochanter ($p < 0.001$), and 1.1% in the total hip compared with baseline ($p = 0.005$). Therefore, zoledronic acid is the only agent that has been shown to reverse bone loss associated with ADT and increase BMD above baseline.

Although there are currently no consensus guidelines for the prevention of CTIBL in patients receiving ADT, treatment algorithms recently published by two independent expert panels both recommend the use of bisphosphonates in men who experience significant bone loss as a result of ADT for prostate cancer [22, 41]. Zoledronic acid appears to be the most promising agent in this setting [42].

The population of patients who are treated with hormonal therapy for breast or prostate cancer may be increasing, and, therefore, CTIBL in these patients is a growing concern. Although there are currently no treatments approved specifically for the prevention of CTIBL, i.v. bisphosphonates have demonstrated significant effects on BMD in patients with early-stage breast or prostate cancer, and zoledronic acid appears to have the greatest potency in these settings. Therefore, the use of bisphosphonates is expected to increase in patients with early-stage breast or prostate cancer.

**Bisphosphonates as Anticancer Therapy**

Bisphosphonates might limit disease progression in bone by indirect and direct mechanisms. Bisphosphonates inhibit osteolysis and tumor-induced osteoclast formation, thereby preventing the release of growth factors from the bone matrix adjacent to malignant bone lesions. Other indirect antitumor mechanisms include inhibition of angiogenesis and activation of γδT cells. These indirect mechanisms could render the bone microenvironment less hospitable to tumor growth. Preclinical evidence suggests that bisphosphonates also have direct antitumor effects, including induction of apoptosis and inhibition of cell proliferation and cell adhesion [5]. Therefore, use of bisphosphonates in patients with locally advanced cancer may alter the course of their disease. Indeed, preliminary clinical evidence from adjuvant trials in the breast cancer setting suggests that bisphosphonates may prevent bone metastasis [43, 44]. Based on a strong preclinical rationale and on preliminary clinical evidence, several clinical trials in breast cancer, prostate cancer, and non-small cell lung cancer (NSCLC) are investigating the potential of potent i.v. bisphosphonates to prevent disease progression in bone and to improve survival.

Evidence from animal models suggests that activation of osteoclast-mediated bone resorption is an essential step in the process of bone metastasis. Mice with defects in osteoclast activation fail to develop bone metastases when inoculated with prostate tumor cells [45]. Moreover, mice with increased osteolysis after surgical castration develop more bone metastases when inoculated with the hormone-independent prostate cancer cell line PC-3 than intact control mice [46]. Notably, this animal model reflects the situation in men who are developing hormone-refractory disease while receiving ADT for prostate cancer. Therefore, reducing bone resorption may help to prevent bone metastasis.

Bisphosphonates also have demonstrated direct antitumor effects on a variety of human cancer cell lines in vitro and reduced tumor burden in bone in animal models of breast and prostate cancer [47]. Although antitumor effects have been reported for many bisphosphonates, zoledronic acid has demonstrated the most potent effects in the broadest range of tumor models. Zoledronic acid can impede the growth and invasiveness of tumor cells and induce apoptosis in human breast and prostate cancer cell lines [48-51]. Zoledronic acid has also shown synergistic antitumor effects when combined with paclitaxel (Taxol®; Bristol-Myers Squibb; Princeton, NJ) [52], docetaxel (Taxotere®; Aventis Pharmaceuticals Inc.; Bridgewater, NJ) [53], and other cytostatic agents [54-56]. In animal models of breast cancer and prostate cancer, zoledronic acid has been shown to inhibit bone metastasis, reduce the size of established bone lesions, and significantly reduce tumor-induced osteolysis [51, 57, 58].

**Clinical Trials of Bisphosphonate Anticancer Effects**

Early clinical trials in patients with advanced breast cancer without bone involvement suggested that oral clodronate could prevent bone metastasis. Kanis et al. [59] investigated oral clodronate (1,600 mg/day) in patients with early-stage breast cancer ($n = 133$) and reported that the mean number of bone lesions per patient was lower in the clodronate group than in the placebo group, although clodronate did not significantly reduce the proportion of patients who developed bone metastases. More recently, several large, long-term clinical trials have provided conflicting evidence of the clinical antitumor effects of oral clodronate (Table 3) [43, 44, 60-63]. Diel et al. [43] reported the results of a single-institution trial demonstrating that daily oral clodronate for 2 years significantly reduced the incidence of bone metastases and significantly improved survival compared with placebo. Re-analysis of the patients after 103 months (±12 months) revealed that clodronate-treated patients had a lower incidence of osseous
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and visceral metastases and significantly better overall survival ($p < 0.01$) [61]. However, subsequent long-term multicenter trials reported by Saarto et al. [60, 63] and Powles et al. [44, 62] have produced inconsistent results. Although Powles et al. [44] did report a significantly lower incidence of bone metastases after 2 years in patients treated with oral clodronate compared with those treated with placebo, there were no significant differences in the incidence of bone or visceral metastases after a median follow-up of 5.5 years. However, the risk of bone metastases was significantly lower for the clodronate-treated patients at the 2-year ($p = 0.031$) and 5-year time points ($p = 0.043$), and overall survival was significantly better for the clodronate group ($p = 0.048$) [62]. In contrast, in the study reported by Saarto et al. [60], oral clodronate had no significant effect on the incidence of bone metastasis. And, in fact, the incidence of visceral metastases was significantly higher and the median survival was significantly shorter in the clodronate group than in the placebo group after a median follow-up of 5 years. After 10 years of follow-up, the incidence of nonskeletal recurrences was still significantly higher in patients who had received clodronate than in those who received placebo, but the difference in overall survival was no longer significant [63].

For example, in randomized clinical trials in patients with bone metastases from breast cancer, pamidronate (90 mg every 3–4 weeks) had a higher rate of bone lesion regression than placebo [64], and zoledronic acid was recently shown to significantly prolong the median time to bone lesion progression in patients with bone metastases secondary to renal cell carcinoma [65]. Therefore, potent i.v. bisphosphonates may have significant antitumor effects in the clinical setting and thereby prevent bone metastasis.

### Clinical Trials for the Prevention of Bone Metastases

In the early breast cancer setting, trials are ongoing to investigate the efficacy of clodronate, risedronate, and zoledronic acid in conjunction with standard anticancer therapy for the prevention of bone metastases. The 3-year National Surgical Adjuvant Breast and Bowel Project (NSABP) B34/CTSU trial is comparing the effects of 1,600 mg/day oral clodronate with those of placebo on disease progression in 3,400 patients with stage I or II breast cancer. The 5-year Adjuvant Zoledronic Acid to Reduce Recurrence (AZURE) trial will accrue 3,300 patients with stage II or III breast cancer and no evidence of metastatic disease and will assess disease-free survival and time to bone and distant metastasis in patients treated with standard anticancer therapy alone and in those treated with standard therapy plus zoledronic acid (4 mg), administered monthly for 6 doses, every 3 months for eight doses, and then every 6 months for five doses. Other end points include overall survival and incidence of skeletal morbidity. The Southwest Oncology Group (SWOG) is also conducting a large randomized 3-arm trial (SWOG 0307) to compare the effects of i.v. zoledronic acid (4 mg via a 15-minute i.v. infusion every month for six doses, then every 3 months), oral clodronate (1,600 mg/day), and oral ibandronate (Bondronat®; Hoffmann-La Roche Inc.; Nutley, NJ; 50 mg/day) on disease-free survival in patients with stage I, II, or IIA breast cancer (targeted accrual = 6,000 patients). Secondary end points include overall survival, BMD, quality of life, and bone markers as predictors of recurrent disease.

Clinical trials are also investigating the potential benefits of zoledronic acid for the prevention of bone metastasis in patients with prostate cancer. These patients are at a high risk for developing bone metastases. Ongoing or planned clinical trials include a collaborative trial among the European Association of Urology (EAU), the Scandinavian Prostate

### Table 3. Clinical trials of oral clodronate for the prevention of bone metastases

<table>
<thead>
<tr>
<th>Trial</th>
<th>n of patients</th>
<th>Duration (years)</th>
<th>Treatment</th>
<th>Median follow-up</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Diel et al.</em> [43, 61]</td>
<td>302</td>
<td>2</td>
<td>3</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td><em>Saarto et al.</em> [38, 63]</td>
<td>299</td>
<td>3</td>
<td>5.0</td>
<td>0.035</td>
<td></td>
</tr>
<tr>
<td><em>Powles et al.</em> [44, 62]</td>
<td>1,069</td>
<td>2</td>
<td>5.5</td>
<td>0.043</td>
<td></td>
</tr>
</tbody>
</table>

All trials compared oral clodronate (1,600 mg/day) with placebo.

*Comparison favored placebo over oral clodronate.

Abbreviation: NS = not significant.
Cancer Group (SPCG), and the German Arbeitsgemeinschaft Urologische Onkologie (AUO) group (CZOL446GDE08) and studies by the Central European Cooperative Oncology Group (CECOG; CZOL446EAT03, which has a design similar to that of the multigroup trial), the Medical Research Council (MRC; CZOL446G2411: MRC/STAMPEDE), and the Trans-Tasman Radiation Oncology Group (TROG; CZOL446G2405: RADAR). Clinical trials are also investigating the antitumor effects of zoledronic acid in patients with other solid tumors who are at risk for bone metastasis. For example, the CZOL446G2419 trial is enrolling patients with NSCLC, and a study is planned in patients with renal cell carcinoma.

CONCLUSIONS

Bisphosphonates have demonstrated significant clinical benefit in a range of diseases of bone metabolism and for the prevention of skeletal complications from malignant bone disease. In addition, bisphosphonates appear promising for the prevention of CTIBL in patients with breast or prostate cancer receiving estrogen- or androgen- ablative hormonal therapies. Zoledronic acid has demonstrated the broadest range of clinical activity and the greatest promise for the prevention of CTIBL. Zoledronic acid and other bisphosphonates are currently being investigated for the prevention of CTIBL in patients with breast or prostate cancer. Moreover, bisphosphonates have demonstrated antitumor activity in preclinical models, and clinical evidence suggests that bisphosphonates may slow the progression of bone lesions or prevent bone metastasis [47]. Therefore, trials are ongoing to determine the clinical antitumor effects of bisphosphonates in patients with early-stage breast cancer, prostate cancer, NSCLC, and renal cell carcinoma. The results of those trials will provide important insight into the optimal timing and modality of bisphosphonate therapy in those patient populations. The clinical applications for bisphosphonates in the oncology setting are likely to expand further as these trials mature.

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