Bisphosphonates in Oncology: Rising Stars or Fallen Heroes

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ABSTRACT
The introduction of bisphosphonates in oncology has dramatically changed the management of patients with metastatic bone disease. In this manuscript, we thoroughly scrutinize the available body of clinical trials supporting the use of bisphosphonates in this setting and review new and ongoing research. Additionally, we summarize the data showing the benefits of bisphosphonate use in the prevention of treatment-induced bone loss and the intriguing emerging evidence on the antitumor potential of some of these agents when used in the adjuvant setting. Finally, we address the need for a careful consideration of potential benefits of bisphosphonate therapy and the risk for osteonecrosis of the jaw, a recently recognized late-toxicity of their use. The Oncologist 2009;14:181–191

INTRODUCTION
Recently, the 40th anniversary of the publication of a landmark paper by Herbert Fleisch and colleagues in 1968 passed, describing the in vitro and in vivo influence of bisphosphonates—erroneously called diphosphonates at that time—on the precipitation and dissolution of calcium phosphate [1, 2]. This research paved the way to the study of the effects of these agents on hydroxyapatite, and their first therapeutic application in a patient with myositis ossificans just 1 year later [3, 4]. In oncology, the introduction of bisphosphonate therapy has radically improved the management and prevention of skeletal-related events (SREs) associated with malignancy disseminated to the bones, including pathologic fractures, bone pain, impaired mobility, spinal cord compression, and hypercalcemia [5, 6].

Also, it is approximately 5 years ago that Robert Marx published a letter alerting the medical community to the increase in the number of patients presenting with nonhealing areas of exposed bone in the oral cavity. He termed the condition “osteonecrosis of the jaw” (ONJ) and noted that all these patients apparently shared a common denominator: bisphosphonate treatment [7]. Although the safety profile of the bisphosphonates was, until that time, considered to be favorable and well-understood, successive case series seemed to confirm this particular association, as previously reported in this journal [8–10].

Both the recognition of ONJ as a late toxicity of
biphosphonate treatment and the recent advances in basic and clinical research into the effects of biphosphonate therapy in different malignancies warrant an update to redefine the balance of risks and benefits.

CURRENT EVIDENCE SUPPORTING THE USE OF BIPHOSPHONATES IN CANCER

Multiple Myeloma
The older non-nitrogen-containing clodronate and the more potent amino- bisphosphonates pamidronate, ibandronate, and zoledronic acid have been studied in multiple myeloma. Two large, placebo-controlled trials with oral clodronate are of interest, next to a larger number of smaller and mostly uncontrolled studies. One trial, using 2,400 mg/day for 24 months (n = 350), concluded a 50% proportional lower number of patients with progression of osteolytic bone lesions (24% versus 12%; p = .026) and found more patients attaining a pain-free state [11]. Patients in the second placebo-controlled clodronate trial (n = 536) received 1,600 mg/day and showed, at 1 year, a 50% lower occurrence of severe hypercalcemia (5% versus 10%; p = .06) and number of reported nonvertebral fractures (6.8% versus 13.2%; p = .04) [12].

In contrast, only one placebo-controlled trial has been conducted with i.v. pamidronate (90 mg 4 weekly) in stage III multiple myeloma patients (n = 392) with at least one osteolytic lesion, showing, at 9 months, a significantly lower proportion of patients with an SRE (24% versus 41%; p < .001) and a lower mean number of SREs per year (1.1 versus 2.2; p = .0006) [13]. However, a subsequent placebo-controlled study with oral pamidronate (300 mg/day) demonstrated no significant effect on SREs, presumably because of its very low and variable bioavailability [14].

In addition to a randomized phase II dose-seeking comparison with pamidronate (n = 280) demonstrating equal efficacy, the results of one randomized phase III trial (n = 518), showing the noninferiority of zoledronic acid versus pamidronate, form the basis for the use of this potent bisphosphonate in multiple myeloma. Both trials recruited a mixed population of breast cancer and stage III multiple myeloma patients [15, 16].

Finally, a large phase III trial with i.v. ibandronate (2 mg monthly) was negative, with no difference in bone morbidity or survival in stage II/III multiple myeloma patients [17].

Breast Cancer
Little new research has been performed in the last decade in the setting of bone metastatic breast cancer, with major research groups focusing on adjuvant bisphosphonate therapy instead. In metastatic disease, early evidence from three placebo-controlled trials (total n = 417) suggests that oral clodronate (800 mg/day or 1,600 mg/day) resulted in a significantly lower number/rate of skeletal events (hazard ratio [HR], 0.84; 95% confidence interval [CI], 0.72–0.98), longer time to first SRE, lower incidence of vertebral fractures and deformity, and lower total number of (terminal) hypercalcemic episodes, and leads to less pain and a lower use of analgesics (Fig. 1) [18–21].

However, the methodology used in one of these studies may have overestimated treatment effects [18], the subsequent availability of more robust data demonstrating similar activity of pamidronate, and the lack of U.S. Food and Drug Administration approval in the U.S. have all contributed to the rather limited use of clodronate in these patients [22]. Indeed, four placebo-controlled trials (n = 1,453) concluded that i.v. pamidronate (45–90 mg 3–4 weekly) results in a significantly longer time (12.7 versus 7.0 months; p < .001) to the occurrence of the first SRE (HR, 0.77; 95% CI, 0.69–0.87), lower incidence of SREs (53% versus 68%; p < .001), and longer time to progression of bone lesions (8.3 versus 5.6 months; p = .02) [21, 23–27]. Moreover, evidence from a head-to-head comparison suggests its superiority over clodronate in both controlling symptoms and suppressing bone resorption [28].

The most recent data available are on the newer bisphosphonates zoledronic acid and ibandronate. Besides the previously cited phase II trial in a mixed population of breast cancer and multiple myeloma patients, the firm body of evidence supporting zoledronic acid comes from both a positive placebo-controlled trial (n = 228) and a phase III noninferiority head-to-head comparison with pamidronate in patients with predominantly breast cancer (n = 1,130) [16, 29]. At 1 year of follow-up and excluding hypercalcemia of malignancy, zoledronic acid resulted in a 20% lower percentage of patients with at least one SRE (30% versus 50%; p = .003), 39% lower rate of SREs (p = .027), longer median time to first SRE (median, not reached versus 12 months; p = .007), and 41% lower risk for SREs in a multiple-event analysis (HR, 0.59; 95% CI, 0.37–0.91; p = .019), compared with placebo [29]. Furthermore, zoledronic acid was found to provide a 20% additional lower risk for skeletal events (HR, 0.80; 95% CI, 0.65–0.98; p = .037) compared with pamidronate (multiple-event analysis), and even greater benefit in patients with at least one osteolytic lesion [30]. Additional evidence suggesting the superiority of zoledronic acid comes from a phase II study showing that zoledronic acid, used as a salvage therapy in patients failing clodronate or pamidronate, can significantly improve pain control [31].

The oral and i.v. use of ibandronate has been studied in
three placebo-controlled trials, all using a primary efficacy parameter that hampers comparison of the results with other studies. The skeletal morbidity period rate (SMPR) was defined as the number of 12-week periods with new bone complications divided by the number of periods on study, and excluding SREs that occurred during the first 12 weeks.

The i.v. trial (MF4265) randomized 466 patients to ibandronate (2 mg or 6 mg) or placebo every 3–4 weeks for up to 2 years. Only the group receiving 6 mg showed a statistically significant advantage in terms of the SMPR ($p = 0.004$), the number of new bone events, and the time to first event [32]. The efficacy of oral ibandronate was reported in a pooled analysis of two smaller phase III trials (MF4434 and MF4414) randomizing patients with bone metastases from breast cancer to 50 mg/day ibandronate ($n = 287$) or placebo ($n = 277$) for up to 96 weeks. It concluded that ibandronate produced a significantly lower mean SMPR (0.95 versus 1.18; $p = 0.004$), lower risk for a skeletal event (HR, 0.62; 95% CI, 0.48–0.79; $p = 0.001$), lower mean number of events requiring radiotherapy (0.73 versus 0.98; $p < .001$), and fewer events requiring surgery (0.47 versus 0.53; $p = 0.037$) [33].

However, the difference in the proportion of patients with an SRE, which is a straightforward and conservative endpoint that is considered statistically more rigorous for assessing the clinical benefit of bisphosphonate therapy, was not significant in the i.v. trial (51% versus 62%; $p = 0.052$) and was not reported in the oral trial [34]. Therefore, the results of two ongoing phase III trials comparing ibandronate with zoledronic acid are eagerly awaited [35, 36].

**Prostate Cancer**

In patients with prostate cancer, the effect of clodronate on bone metastasis–free survival in the nonmetastatic setting and bone pain and bone progression–free survival in metastatic disease has been well studied. Although the results from smaller uncontrolled trials had been encouraging, all large controlled studies, with a total of 1,214 patients randomized, have reported negative findings (Table 1) [37].

Similarly, a randomized, prospective, double-blind, placebo-controlled study ($n = 57$) with i.v. etidronate followed by oral maintenance therapy in patients with hormone-refractory metastatic prostatic cancer showed no significant difference in pain control between the two groups [38].

In the treatment and prevention of SREs, pamidronate has been prospectively evaluated with disappointing results as well. A pooled analysis of two multicenter, double-blind, randomized, placebo-controlled trials ($n = 378$) in hormone-refractory prostate cancer patients with bone metastases failed to demonstrate an overall treatment benefit of 3-weekly i.v. pamidronate (90 mg) on self-reported pain

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**Figure 1.** Overview of the benefit of treatment with bisphosphonates over placebo on the risk of a skeletal-related event in bone metastatic breast cancer (hazard ratios with 95% confidence intervals). Pooled data for clodronate and pamidronate are taken from a Cochrane review by Pavlakis et al. [21].

Abbreviation: PO, orally.
measurements, analgesic use, proportion of patients with an SRE, or mobility [39].

Treatment with 3-weekly i.v. zoledronic acid (4 mg), on the other hand, has effectively demonstrated a benefit in hormone-refractory prostate cancer patients with metastatic bone disease. In a large prospective, randomized, controlled trial (n = 422), there was a significant absolute 11% lower proportion of patients who experienced one or more SREs (p = .028) and a significantly longer time until the first SRE of 5.5 months (p = .009). In addition, an absolute lower mean skeletal morbidity rate of 0.7 SREs per year (p = .005) was observed, compared with the placebo group in which at 2 years of follow-up 49% of patients experienced one or more SREs and had on average 1.47 SREs per year [40, 41]. Looking beyond first-event analyses, zoledronic acid also resulted in a 36% lower ongoing relative risk for SREs (HR, 0.64; 95% CI, 0.43–0.81; p = .002), compared with placebo [42]. Interestingly, patients without pain appeared to benefit most, and therefore treatment with zoledronic acid should probably not be postponed until symptoms develop [43].

Data on ibandronate, the latest addition in the constellation of the bisphosphonates, are still maturing, and placebo-controlled trials are required before it can be considered [44].

**Other Solid Tumors**

Data on the efficacy of zoledronic acid in small cell and non-small cell lung cancer, renal cell carcinoma, and a variety of other histologies (including head and neck, thyroid, and unknown primary cancer) are derived from a large (n = 773), placebo-controlled trial demonstrating a significantly lower proportion (39% versus 48%; p = .04) of patients with an SRE (HR, 0.69; 95% CI, 0.54–0.89; p = .003), a longer median time to first SRE (7.9 versus 5.2 months; p = .009), and a 36% lower annual incidence of SREs (mean, 1.74 versus 2.71 SREs per year; p = .01), compared with placebo at 21 months of follow-up [45, 46]. A subset analysis of renal cell carcinoma patients in that trial was in agreement with this, with a significantly lower proportion (37% versus 74%; p = .015) of patients with an SRE (HR, 0.39; 95% CI, 0.19–0.81; p = .008) [47]. The whole of these data has led to zoledronic acid being the only bisphosphonate to have worldwide regulatory approval for use in patients with bone metastases secondary to solid tumors other than breast cancer. Moreover, a randomized phase III study recruiting patients (n = 287) with a broad range of malignancies demonstrated the superiority of zoledronic acid over pamidronate in the treatment of hypercalcemia [48].

**EMERGING EVIDENCE ON THE FUTURE ROLE OF BISPHOSPHONATES IN CANCER**

**Prevention of Treatment-Induced Bone Loss**

The potential benefit of bisphosphonates to prevent the bone loss caused by endocrine therapy in breast and pros-

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**Table 1. Overview of randomized, placebo-controlled trials evaluating the benefit of clodronate in prostate cancer**

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>HRPC</th>
<th>Bone metastases</th>
<th>Intervention</th>
<th>Primary endpoint and result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mason et al. [103]</td>
<td>508</td>
<td>No</td>
<td>No</td>
<td>Clodronate, 2,080 mg/day PO</td>
<td>Bone metastases-free survival: HR, 1.22; 95% CI, 0.88–1.68; p = .23</td>
</tr>
<tr>
<td>Dearnaley et al. [104]</td>
<td>311</td>
<td>No</td>
<td>Yes</td>
<td>Clodronate, 2,080 mg/day PO</td>
<td>Bone progression-free survival: HR, 0.79; 95% CI, 0.61–1.02; p = .06</td>
</tr>
<tr>
<td>Ernst et al. [105]</td>
<td>209</td>
<td>Yes</td>
<td>Yes</td>
<td>Clodronate, 1,500 mg/3 wks i.v.</td>
<td>Pain score reduction: response in 45% versus 39%; p = .54</td>
</tr>
<tr>
<td>Kylmala et al. [106]</td>
<td>56</td>
<td>Yes</td>
<td>Yes</td>
<td>Clodronate, 300 mg/day i.v. 5 days, then 1,600 mg/day PO 12 mos</td>
<td>Pain intensity using VAS: no significant difference in VAS at 1, 3, 6, or 12 mos</td>
</tr>
<tr>
<td>Strang et al. [107]</td>
<td>55</td>
<td>Yes</td>
<td>Yes</td>
<td>Clodronate, 300 mg/d i.v. 3 days, then 3,200 mg/day PO 3 wks</td>
<td>Pain intensity using VAS: 21 mm difference in VAS; p &gt; .05</td>
</tr>
<tr>
<td>Elomaa et al. [108]</td>
<td>75</td>
<td>Yes</td>
<td>Yes</td>
<td>Clodronate, 3,200 mg/day PO 1 mo, then 1,600 mg/day PO</td>
<td>Proportion of patients with pain: no significant difference between groups at 1, 3, or 6 mos</td>
</tr>
</tbody>
</table>

**Abbreviations:** CI, confidence interval; HR, hazard ratio; HRPC, hormone-refractory prostate cancer; PO, orally; VAS, visual analogue scale.
tate cancer has previously been reviewed in this journal [49].

In summary, androgen-deprivation therapy (ADT) in prostate cancer patients leads to a clinically significant bone loss that translates into a higher fracture risk at 5 years of 19.4%, compared with 12.6% in nonusers (p < 0.001) [50, 51]. Placebo-controlled trials have shown that pamidronate (60 mg i.v. every 3 months) can maintain bone mineral density (BMD) in patients (n = 43) with nonmetastatic prostate cancer receiving a gonadotropin-releasing hormone agonist, and that oral alendronate (70 mg once weekly) not only prevents bone loss but actually improves BMD in patients (n = 112) on ADT [52, 53].

However, zoledronic acid (4 mg i.v. once or every 3 months) currently has the most impressive bulk of evidence, with four published randomized controlled trials (n = 439) consistently demonstrating an increase in BMD, even after a single administration [54–57].

Likewise, breast cancer patients with chemotherapy-induced ovarian failure or receiving aromatase inhibitor treatment have a greater annual bone loss that results in a higher fracture incidence (11%) than in patients treated with tamoxifen (8%) [58, 59]. Previous studies into the benefit of bisphosphonate treatment in these patients have shown that the oral bisphosphonates clodronate (n = 148) and risedronate (n = 53) can reduce this bone loss, but not completely prevent it [60, 61].

The most convincing results, however, are available for zoledronic acid, with three randomized trials (n = 2,068), providing evidence that zoledronic acid (4 mg i.v. every 6 months) effectively inhibits aromatase inhibitor–associated bone loss. Moreover, in postmenopausal women with early-stage breast cancer receiving letrozole, upfront zoledronic acid prevents bone loss more effectively than when treatment is delayed until bone loss has been documented [62, 63].

Prevention of Bone Metastases

With nearly every trial with bisphosphonates in patients with skeletal metastases from breast cancer being positive, studies investigating the impact of clodronate on metastasis-free and overall survival in patients without bone metastases have produced very conflicting results, with two positive and one negative randomized trial [64–67]. A recent meta-analysis of these trials concluded that there was no evidence to suggest that adjuvant clodronate therapy improves 5-year overall (HR, 0.75; 95% CI, 0.31–1.82), bone metastasis-free (HR, 0.68; 95% CI, 0.38–1.23), or nonskeletal metastasis-free (HR, 0.89; 95% CI, 0.40–1.98) survival in breast cancer patients [68]. Hopefully, a more definitive judgment on clodronate can be rendered when the eagerly awaited National Surgical Adjuvant Breast and Bowel Project B34 trial, which has accrued 3,000 patients, investigating adjuvant oral clodronate in patients with resected stage I–II breast cancer, has accumulated enough events to be reported, probably later this year [69].

The effect of newer and more potent bisphosphonates on disease-free and overall survival in this setting is actively being investigated. A large open-label study, randomizing 953 women with primary breast cancer to either adjuvant oral pamidronate (150 mg twice daily for 4 years) or no bisphosphate, failed to demonstrate a beneficial effect on the occurrence of bone metastases [70]. In contrast, zoledronic acid has shown very promising antitumor activity in preclinical animal and in vitro research, as well as synergistic effects with the sequential administration of chemotherapy [71, 72]. Recently, the exciting first efficacy results of the Austrian Breast and Colorectal Cancer Study Group Trial 12 have been reported, suggesting that the use of adjuvant zoledronic acid can improve disease-free survival (DFS) in premenopausal women who are receiving endocrine treatment with ovarian suppression and tamoxifen or anastrozole. This open-label, multicenter study investigated whether anastrozole is superior to tamoxifen in these patients, and whether adding zoledronic acid to endocrine therapy improves the outcome over endocrine therapy alone (Fig. 2). After a median follow-up of 60 months, there was no statistically significant difference in DFS between the tamoxifen (65 events) and anastrozole (72 events) groups (HR, 1.10; 95% CI, 0.79–1.54; p = .59).

However, women who received zoledronic acid had significantly fewer DFS events (54 versus 83) than those who had not received the bisphosphonate (HR, 0.64; 95% CI, 0.46–0.91; p = .01). Intriguingly, this benefit of zoledronic acid treatment was not only limited to the bone but also resulted in a lower incidence of contralateral breast cancer, locoregional recurrence, and distant nonbone recurrence [73].

Equally promising results have been reported in an early subset analysis of the Breast International Group 1–04/Does Adjuvant Zoledronic acid redUce REcurrence study. This large, multicenter trial randomized a total of 3,360 women with stage II–III breast cancer to standard (neo)adjuvant therapy alone or combined with zoledronic acid (monthly for 6 months, then every 3 months for 2 years, then every 6 months for 2.5 years) with a planned follow-up of 5 years [74]. In the 205 women who received neoadjuvant chemotherapy, the addition of zoledronic acid significantly improved the pathological response rate of the primary tumor [75]. Whether these benefits will impact disease-free survival is yet to be reported.

Finally, of the other ongoing adjuvant bisphosphonate trials, including GAIN (German Adjuvant Intergroup Node-positive) (n = 3,000) and ICE (Ibandronate with or without
Capecitabine in Elderly patients) (n = 1,400), the Southwest Oncology Group S0307 study that started recruitment in 2005 is of particular interest. This ambitious phase III, randomized trial is seeking to recruit 4,500 participants, comparing adjuvant zoledronic acid (4 mg i.v. monthly for 6 months, then 3 monthly for 2.5 years) with clodronate (1,600 mg/day orally [PO] for 3 years) and with ibandronate (50 mg/day PO for 3 years) in patients with resected stage I–III breast cancer, and follow them for 10 years [76].

IMPACT AND PREVENTION OF ONJ
ONJ has officially been defined by consensus as the persistence of exposed bone in the oral cavity, despite adequate treatment for 8 weeks, without local evidence of malignancy and no prior radiotherapy to the affected region [77].

Our current understanding of the underlying pathophysiology is limited, but in particular, the potent nitrogen-containing bisphosphonates have been associated with this rare disorder, suggesting that their powerful inhibition of bone resorption and the subsequent reduction in remodeling capacity are important. Additionally, in approximately 80% of patients with ONJ, an invasive dental procedure was performed at the affected site, implicating trauma as a pivotal factor in the disease etiology [78]. Nonetheless, other factors, including superinfection, inhibition of angiogenesis by bisphosphonates or concomitant treatments, and impaired wound healing resulting from cytotoxic or steroid therapy, have been suggested to play a role as well [79].

Current estimates on the prevalence of ONJ in bisphosphonate-treated multiple myeloma patients vary between 2.3% and 11%, with smaller series and Greek authors [80–82] reporting higher numbers than in larger retrospective cohort studies [9, 83] or studies originating from other parts of the world. Despite this broad range, this risk does seem consistently higher than the 1.2%–6.5% reported for breast or prostate cancer patients (Table 2). The cause of this greater susceptibility remains unknown, although some evidence suggests a higher incidence of dental problems requiring surgery in myeloma patients. In addition, the longer duration of remissions in comparison with other malignancies may increase the prevalence of ONJ, as well as regional differences in oral comorbidities [84].

In response, existing treatment guidelines published by the American Society of Clinical Oncology (ASCO) and the Mayo Clinic have been revised, suggesting a limit to the duration of bisphosphonate therapy of 2 years in patients who respond to therapy or have stable disease, instead of continued use until there is evidence of a substantial decline in a patient’s general performance status [85–87]. The results of LOTUZ (LOng-Term Use of Zometa), an ongoing, multicenter, prospective, pharmacoepidemiological trial studying the safety and efficacy of the long-term use of zoledronic acid beyond 2 years in patients with solid and hematologic malignancies, will probably provide valuable data to assess the strength of this recommendation [88].

Also, a lower frequency of bisphosphonate administration (e.g., 3 monthly) has been suggested in patients who have minimal disease requiring active therapy, although no trial data on efficacy and effect on ONJ occurrence exist to support this claim [86]. An even more controversial topic is the preferred bisphosphonate in myeloma patients, with ASCO suggesting either pamidronate or zoledronic acid and the Mayo Clinic choosing the former as the agent of choice in newly diagnosed patients [86, 87]. Indeed, some cohort studies have suggested a higher risk for ONJ in patients treated with zoledronic acid, compared with pamidronate [9, 80]. However, uncertainties regarding the statistical validity of one such report exist [89], whereas another had an unusually high incidence of ONJ [82], and more recent reports studying a larger number of patients could not replicate this finding [83]. Moreover, most of these reports were published before adequate prevention strategies for ONJ were implemented and prior to the publication of a consensus definition of ONJ.

Indeed, the only intervention with a proven benefit in reducing the occurrence of ONJ is prevention, effectively reducing the incidence of ONJ in one study from 3.2% to 1.3% in patients with solid tumors [90]. Similar benefits have also been reported in multiple myeloma patients [91]. Recent data emerging from ongoing prospective trials with
Zoledronic acid have been rather reassuring and did not document any case of ONJ [63, 73].

Consensus-based prevention guidelines recommend a panoramic radiograph to help in the diagnosis of caries and periodontal disease, the evaluation of third molars, and the identification of metastatic cancer and other bony pathology [92]. If bisphosphonate therapy can be delayed, preventive surgery to eliminate potential sites of infection should be performed. Only after the mucosa has completely healed should bisphosphonate therapy be started. Finally, dentures should be adjusted to relieve pressure on mucosal surfaces.

Optimal dental health during treatment is essential, and all patients should be informed of the importance of good oral hygiene and the use of chlorhexidine rinses. In addition, regular visual inspections by the treating physician and routine assessments (at least annually) by a dental specialist are warranted.

Whenever dental treatment is necessary, the less invasive endodontic techniques with preservation of the dental root are preferred over total tooth extraction. Only when teeth have a mobility score ≥3 should extraction be considered, and it should be performed asatraumatically as possible [92]. To prevent local infection, the use of antibiotics may be indicated. Otherwise, any elective jaw procedure requiring bone healing should be avoided.

Some authors suggest the withdrawal of bisphosphonate therapy for 1–3 months before performing invasive dental procedures [86, 93]. Considering the long half-life of bisphosphonates in bone, however, it remains doubtful if adequate osteoclast recovery is realistic [94].

**Risk Stratification Using Bone Turnover Markers**

When bone is resorbed by osteoclast activity, the collagen remnants of the organic matrix can be detected in the serum or urine [95]. These degradation products, including the aminoterminal (NTX-I) and carboxyterminal (CTX-I) crosslinked telopeptide, have been shown to be specific biochemical markers of osteoclast function and hence of bone turnover [96]. Although initially used in clinical trials to assess the effect of bisphosphonate therapy on bone turnover, the use of serum CTX-I has recently been proposed to predict the risk for ONJ after an invasive dental procedure in patients receiving oral bisphosphonate therapy. Patients with morning fasting serum CTX-I levels ≥150 pg/ml are considered to have adequate residual bone remodeling capacity and to be only at minimal risk of developing ONJ [97].

However, the technique is subject to considerable variability, both subject and assay related, and most patients on bisphosphonate therapy will not have had a baseline CTX-I measurement. Moreover, known sources of CTX-I variability include, amongst others, the circadian cycle, gender, age, food intake, renal and liver function, and concomitant medication use [98]. Therefore, it can be questioned whether an arbitrarily defined cutoff of 150 pg/ml that does not take into account pretherapy baseline CTX-I levels is universally appropriate. In fact, recently published reports cast doubt on the reliability of CTX-I by failing to demonstrate a significant relationship between the marker and the severity of ONJ and the fact that some patients with ONJ have bone markers that are within the normal range [99, 100].

In patients with skeletal metastases, the theoretical merit of bone turnover markers is lacking, and they should thus not be used to guide clinical management decisions. Indeed, bone markers give an overall impression of bone turnover in the whole skeleton, and in cancer patients this will largely be determined by the number and activity of...
metastatic tumor deposits in the skeleton. A serum CTX-I sample with a value above a predefined threshold is, in these patients, not a measure of adequate residual osteoclast capacity, but rather of poor disease control.

In addition, the increase in bone turnover markers caused by skeletal metastases varies greatly among different malignancies. This was elegantly demonstrated in a pooled analysis of three randomized, controlled, phase III clinical trials of cancer patients (n = 1,462) receiving zoledronic acid. Approximately 44% of prostate cancer patients had highly elevated urinary NTX-I/creatinine levels at baseline, compared with 37% of breast cancer patients and only 20% of multiple myeloma patients. Moreover, bone resorption markers have been found to provide prognostic information in patients with bone metastases. Persisting high or moderate NTX-I/creatinine levels in patients with solid tumors during bisphosphonate treatment were associated with a 4.8-fold (95% CI, 3.9–5.9; p < .001) and 3.1-fold (95% CI, 2.5–3.8; p < .001) higher risk for death, respectively, compared with patients with low bone turnover markers [101]. Consequently, the use of marker-directed therapy is prospectively being investigated in the BISMARK (BISphosphonates in metastatic bone disease: MARKer directed therapy with zoledronic acid) trial [102].

In summary, although the theoretical concept of risk stratification using CTX-I in osteoporosis patients is appealing, the current evidence is still limited and requires further validation before its widespread clinical use is warranted. In contrast, in cancer patients with metastatic bone disease, who will ultimately represent 95% of ONJ cases, we see no role for bone markers to guide management decisions as yet.

CONCLUSION

The bisphosphonates have been proven to be an important asset in the treatment and prevention of SREs in cancer patients with bone metastases. Although the results in the adjuvant setting are very promising, in particular in the prevention of bone metastases, they are as yet not practice changing. With the results of a number of large trials set to be reported in the near future, the final verdict on the adjuvant use of bisphosphonates in breast cancer is still out. Nonetheless, it seems reasonable to assume that some of this research will translate into new indications for bisphosphate use in oncology.

With the increasing use of bisphosphonates, ONJ has to be recognized as a potential side effect that is rare, but can have a high impact on quality of life. However, when implementing a set of straightforward preventative measures, ONJ should not deter the clinician from using this powerful tool in daily practice and recognizing the rising stars that the bisphosphonates continue to be in oncology.

AUTHOR CONTRIBUTIONS

Conception/design: Tim Van den Wyngaert
Collection/assembly of data: Tim Van den Wyngaert
Data analysis: Tim Van den Wyngaert, Manon T. Huizing, Eric Fossion, Jan B. Vermorken
Manuscript writing: Tim Van den Wyngaert
Final approval of manuscript: Manon T. Huizing, Eric Fossion, Jan B. Vermorken

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