Systemic Therapy for Bone Metastases
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Background: Accelerated bone loss in patients with cancer is a frequent problem that may result from invasion of the cancer to bone, paraneoplastic tumor proteins, and/or hormonal therapies utilized for cancer treatment. Patients with osteolytic bone disease from multiple myeloma and bone metastases from solid tumors may develop a vicious cycle of bone destruction involving both osteolytic and osteoblastic effects. Consequently, a variety of skeletal-related events (SREs) may occur, including pathological fractures, hypercalcemia, spinal cord compression, and the need for surgical intervention and radiation therapy.

Methods: This article reviews the results of trials that investigated the safety and efficacy of pharmacologic agents, including bisphosphonates and denosumab, for treatment of bone metastases. This analysis is derived from an assessment of the medical literature.

Results: Beneficial systemic therapies for bone metastases have been developed to decrease SREs. Possible antitumor effects of the bisphosphonates are explored. In addition, the utility of markers of bone turnover in relation to response to therapy and survival, the safety and toxicity of bone-targeted therapies, treatment guidelines, and economic considerations are also discussed.

Conclusions: Effective systemic therapies for metastatic bone disease are available. Ongoing and future research projects in this field are also presented.

Introduction
Accelerated bone loss in patients with cancer is a frequent problem that may result from invasion of the cancer to bone, paraneoplastic tumor proteins, and/or hormonal therapies utilized for cancer treatment.1 Hormonal therapies are often employed to treat patients with breast and prostate cancers. Invasion of cancer to bone is a common complication in patients with advanced disease, ranging from 20% to 25% in kidney cancer to 65% to 75% in breast and prostate cancers, and almost all patients with multiple myeloma (70% to 95%) experience invasion of cancer to bone.1,5

In this setting of osteolytic disease from multiple myeloma or bone metastases from solid tumors, metabolically active tumor cells invade and populate bone and secrete growth factors that affect bone resorption and formation by stimulation of osteoclasts, cells that destroy bone by attacking the mineralized bone matrix. Osteoclasts also secrete growth factors that induce tumor cells in the bone to grow, spread, and stimulate the
activity of osteoblasts, cells responsible for the formation of bone. However, osteoblastic activity creates new bone formation away from the sites of osteolytic bone resorption, so weakened areas are not strengthened by osteoblastic activity.4,6 Osteoblasts also release receptor activator of nuclear factor κB ligand (RANKL), a key mediator of osteoclast formation, function, and survival.7 Thus, patients with osteolytic disease from multiple myeloma or bone metastases from solid tumors may develop a vicious cycle of bone destruction involving both osteolytic and osteoblastic effects.1-7

Accordingly, skeletal-related events (SREs) may ensue from increased bone destruction, including pathological fractures, hypercalcemia, spinal cord compression, and the need for surgery and radiation therapy to bone. These occurrences profoundly affect the loss of autonomy, create significant morbidity, and cause bone pain in addition to tremendously increasing health care costs.1,3-5 These complications are also related to shortened survival and deterioration of quality of life.8

Untreated patients with bone metastases are at risk for multiple SREs within a single year, ranging from 1.5 events for prostate cancer to 4.0 for breast cancer.9-12 Development of more effective treatments for metastatic cancers and multiple myeloma has affected tumor response, but improved systemic therapies for bone metastases, in particular, which are presented in this review, have also benefitted patients.

**Pharmacologic Agents**

**Bisphosphonates**

Bisphosphonates are unique drugs with an affinity for bone mineral matrix with the ability to inhibit bone resorption. These pharmacologic agents decrease bone resorption and increase mineralization by enter- ing osteoclasts and inhibiting farnesyl diphosphate synthase, a key enzyme in the biosynthetic mevalonate pathway.13,14 Bisphosphonates may also affect bone resorption through the inhibition of osteoclast precursor maturation, induction of apoptosis in mature osteoclasts, inhibition of tumor cell adhesion to bone, and inhibition of inflammatory cytokine production.15-17 Nitrogen-containing bisphosphonates (N-BPs) have the greatest antiresorptive activity.13,14 Based on in vitro studies, zoledronic acid is the most potent aminobisphosphonate15 and is the only intravenous bisphosphate found to be effective in all types of metastatic bone lesions.16

**Denosumab**

Receptor activator of RANKL is expressed on the surface of marrow stromal cells, activated T cells, and osteoblasts. Denosumab is a fully human monoclonal IgG2 antibody that binds to RANKL, thus inhibiting the interaction between RANK and RANKL.17,18 This process results in diminished osteoclast activity, decreased bone resorption, and increased bone mass.17-18 Therefore, denosumab has been approved by the United States Food and Drug Administration (FDA) for treatment of osteoporosis in postmenopausal women.17 In addition, the benefits of denosumab in protecting bone mineral density for postmenopausal women with nonmetastatic breast cancer receiving adjuvant aromatase inhibitors were reported in the Hormone Ablation Therapy in Breast Cancer (HALT-BC) trial.19 Denosumab was approved by the FDA in November 2010 for prevention of SREs in patients with bone metastases from solid tumors, but it is not indicated for the prevention of SREs in patients with multiple myeloma.

**Bone-Targeted Therapy for Tumors With Bone Metastases**

**Breast Cancer**

Approximately 70% of patients with advanced breast cancer experience bone metastases, which may produce poor quality of life and some of the highest rates of SREs.2-3,12 Bisphosphonates are the primary pharmacologic agents most frequently utilized for the prevention of SREs in patients with breast cancer metastatic to bone.

Meta-analyses of phase III placebo-controlled trials of these agents indicated that intravenous bisphosphonates demonstrated superior efficacy in preventing SREs compared with oral bisphosphonates.20 Further, zoledronic acid has been shown to be the most clinically beneficial bisphosphonate to date. A randomized placebo-controlled trial of 228 women with bone metastases from breast cancer found that zoledronic acid significantly reduced the annual SRE rate by 43% (P = .016), decreased the percentage of patients with at least 1 SRE by 20% (P = .003), and delayed the time to development of a first SRE (P = .007) compared with placebo.21

A long-term study of bone metastases from breast cancer or multiple myeloma revealed that zoledronic acid significantly decreased the proportion of patients who required radiation therapy compared with pamidronate (19% vs 24%, respectively; P = .057).22 In the subgroup of breast cancer patients, those treated with zoledronic acid experienced a 40% reduction in the SRE rate compared with pamidronate (P = .125). Zoledronic acid also reduced the risk of any SRE, including hypercalcemia, by an additional 20% compared with pamidronate (P = .025).22,23

Stopeck et al24 reported results on the safety and ef- ficiency of subcutaneous denosumab (120 mg) compared with intravenous zoledronic acid (4 mg) on a monthly basis in 2,046 women with breast cancer metastatic to bone. Denosumab was statistically superior to zoledronic acid in delaying the time to first on-study SRE by 18% (P < .001 noninferiority; P = .01 superiority). Denosumab was also superior to zoledronic acid in delaying the time to first and subsequent (multiple) SREs by 23% (P = .001). The median time to first on-study SRE

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was not reached for the denosumab group. Rates of overall survival, disease progression, and adverse events were similar between groups.24

**Lung Cancer**

In a pivotal placebo-controlled phase III randomized trial, Rosen et al11 studied 773 patients with bone metastases from lung cancer and other solid tumors (excluding breast and prostate cancers). The group who received 4 mg of zoledronic acid every 3 weeks experienced a 9% reduction in SREs compared with the placebo group (P = .039). Zoledronic acid also significantly delayed the median time to first SRE (P = .009) and significantly reduced the annual incidence of SREs (P = .012) compared with placebo.11

Another study investigated the impact of zoledronic acid therapy on survival of patients with lung cancer and bone metastases. Patients with bone pain due to bone metastases received zoledronic acid and standard chemotherapy, and asymptomatic patients with bone metastases received chemotherapy alone. Those treated with zoledronic acid experienced a statistically significant longer median survival (P < .001) and a significantly longer median time to disease progression (P < .001) compared with asymptomatic patients treated with standard chemotherapy alone. There was a significant correlation between the number of cycles of therapy with zoledronic acid and survival (P < .01) and time to disease progression (P < .01).25 These data suggest that zoledronic acid is effective in delaying the onset of SREs and reduces their risk. The results also signify that early intervention and continuous treatment with bone-conserving therapy may provide additional benefits of delay in disease progression and improvement in survival.

A phase III trial of 1,776 patients with bone metastases from solid tumors (excluding breast and prostate carcinomas) and multiple myeloma randomized participants to receive either zoledronic acid or denosumab. Denosumab was as effective as, but not superior to, zoledronic acid in delaying the time to first and subsequent SREs.26

**Prostate Cancer**

Approximately 70% of patients with advanced prostate cancer develop bone metastases.25 Zoledronic acid is the only bisphosphonate that has demonstrated long-term efficacy in patients with prostate cancer and bone metastases. In a 2-year randomized, double-blind trial of patients with prostate cancer and bone metastases, zoledronic acid significantly reduced the proportion of patients with an SRE (P = .028), delayed the median time to first SRE by almost 6 months (P = .009), and decreased the ongoing risk of SREs by 36% (P < .01) compared with placebo.9 Zoledronic acid also reduced bone pain compared with placebo,9,27 but clodronate, pamidronate, and ibandronate have also demonstrated a benefit in relief of bone pain.28 However, zoledronic acid provided a greater likelihood of creating a meaningful reduction in pain scores at measured intervals over a 24-month period compared with placebo (P ≤ .03 for each point).27 Additionally, zoledronic acid reduced the annual incidence of SREs.27

Results were also recently reported from an ongoing randomized, double-blind multicenter study of 1,901 men with prostate cancer metastatic to bone who received either subcutaneous denosumab (120 mg every 4 weeks) or intravenous zoledronic acid (4 mg every 4 weeks). Denosumab was superior to zoledronic acid in delaying the time to first on-study SRE by 18% (P = .008) and decreasing the rates of multiple SREs by 18% (P = .008). Rates of overall survival, time to disease progression, and adverse events were similar for the two groups.29

**Kidney and Bladder Cancers**

Treatment guidelines for patients with bone metastases from renal cell carcinoma and bladder cancer are limited due to the paucity of randomized trials specifically designed to evaluate bisphosphonates in this patient population. However, a retrospective subset analysis of 46 patients with renal cell carcinoma and bone metastases revealed that, when compared with placebo, zoledronic acid significantly reduced the proportion of patients with 1 or more SREs by 38% (P = .011), prolonged the median time to first SRE (P = .007), decreased the rate of skeletal morbidity (P = .009), and reduced the risk of developing an SRE by 58% (P = .010).30-32

Combinations of therapies for metastatic renal cell carcinoma have also shown benefits. A retrospective analysis of 23 patients with renal cell carcinoma who were treated with zoledronic acid in combination with radiation therapy obtained a higher response rate in relief of pain (P = .019), a reduction in the incidence of SREs (P = .003), and a prolonged SRE-free survival (P = .046) compared with those who received radiotherapy alone.30,31

A retrospective analysis of 25 patients with bladder cancer and bone metastases found a reduced risk of any SRE for those treated with zoledronic acid compared with placebo (RR = 0.817; 95% CI = 0.537-1.23; P = .577), but small numbers prevented statistically significant results.34 A prospective, placebo-controlled, randomized trial of 40 patients with bladder cancer and bone metastases determined that zoledronic acid significantly reduced the proportion of patients with ≥ 1 SRE (P = .010), decreased the mean number of SREs (P = .001), and prolonged the median time to first SRE (P = .0001). The risk for developing an SRE was reduced by 59% (P = .008), and bone pain scores also improved (P = .015).35

The findings suggest that zoledronic acid effectively reduces the rate of SREs in patients with bone metasta-
Hypercalcemia of Malignancy

Extensive bone resorption from bone metastases in solid tumors and myeloma bone disease can lead to excessive release of calcium into the blood, with resultant hypercalcemia. Symptoms may include polyuria, gastrointestinal distress, mental confusion and coma, dehydration, and renal insufficiency. Patients with hypercalcemia tend to have more advanced disease, more widespread bone disease, renal failure, and worse outcome than do patients without hypercalcemia. The bisphosphonates zoledronic acid, pamidronate, and ibandronate are the currently approved treatments for hypercalcemia of malignancy.36

A pooled analysis of two randomized controlled clinical trials to evaluate hypercalcemia of malignancy compared 4 mg and 8 mg of zoledronic acid with 90 mg of pamidronate.41 A complete response at day 10 occurred in patients in the 4-mg zoledronic acid group (88.4%; \( P = .002 \)) and in those in the 8-mg zoledronic acid group (86.7%; \( P = .015 \)) compared with pamidronate (69.7%). The median duration of complete response with normal calcium levels was longer, and the mean corrected serum calcium levels were significantly lower at all time points in the patients treated with zoledronic acid. Another study determined that a single infusion of ibandronate (2 mg or 4 mg) was equivalent to pamidronate (15 mg, 30 mg, 60 mg, or 90 mg) in lowering the mean corrected calcium levels on day 4 (76.5% for ibandronate and 75.8% for pamidronate).42

Potential Antitumor Effects of Bisphosphonates

Data from multiple studies suggest that bisphosphonates may directly or indirectly impair multiple processes required for cancer growth and metastases. Bisphosphonates have demonstrated an ability to induce apoptosis in a variety of cancer cell lines. These agents may also inhibit metastases by decreasing tumor cell adhesion, migration, and invasion. Inhibition of angiogenesis is another property associated with bisphosphonates. Furthermore, these pharmacologic agents may modulate the immune system with subsequent antitumor activity.45 Recent research also found that zoledronic acid may exert its antitumor activity by inhibiting mesenchymal stem cell migration and blocking mesenchymal stem cell secretion of factors involved in breast cancer progression.44

In the clinical setting, a potential preventive effect of bisphosphonates was reported in a retrospective analysis of women with osteoporosis who participated in the Women’s Health Initiative Observational Study. Women who received bisphosphonates had a 32% relative reduction \( (P < .01) \) in the risk of breast cancer compared with women without this therapy.45 Similar results were observed in the Breast Cancer in Northern Israel Study, with a 28% reduced risk of breast cancer in postmenopausal women who received bisphosphonates for more than 1 year.46 Further, a recent investigation determined that the use of oral bisphosphonates for more than 1 year was associated with a 59% relative reduction in the risk of colorectal cancer.47

A meta-analysis of clinical trials from 1966 to 2006 compared patients with breast cancer who received up to 3 years of clodronate with patients who did not receive this medication. There were no significant benefits for patients taking clodronate in regard to overall survival, bone metastases-free survival, or nonskeletal
metastases-free survival.48 The Austrian Breast and Colorectal Cancer Study Group trial (ABCSG-12) tested the effect of adding zoledronic acid every 6 months for 3 years to adjuvant endocrine therapy with tamoxifen and goserelin or anastrozole and goserelin in postmenopausal patients with hormone receptor-positive early-stage breast cancer. The addition of zoledronic acid provided a relative 36% reduction in the risk of disease progression (P = .01).39 A recent 6-month follow-up of this study reported a persistent relative 32% benefit in disease-free survival for the patients who received zoledronic acid (P = .009).50

The Zometa-Femara Adjuvant Synergy trials (Z-FAST/ZO-FAST/E-ZO-FAST) compared immediate vs delayed zoledronic acid in postmenopausal women with early-stage breast cancer who received adjuvant letrozole. The Z-FAST trial determined a 20% relative reduction in risk of disease recurrence for the immediate-treated zoledronic acid group. The ZO-FAST study found a 41% relative decrease in disease recurrence. However, conflicting results were reported for the E-ZO-FAST trial (N = 527), with 19 vs 11 recurrences in the immediate and delayed arms, respectively (hazard ratio [HR] = 1.76; 95% confidence interval [CI] = 0.83, 3.69).51

Another investigation determined that current bisphosphonate use, especially with alendronate, was associated with a substantial 59% reduction in the risk of contralateral breast cancer in patients with estrogen receptor-positive breast cancer.52 The risk of contralateral breast cancer declined further with longer duration of bisphosphonate use.52 However, recent results from the AZURE trial failed to demonstrate an overall benefit for the addition of zoledronic acid to adjuvant chemotherapy or endocrine therapy in patients with breast cancer.53 Definitive recommendations for the use of bisphosphonates in the adjuvant setting will require further study and follow-up data.

The issue of potential risk of esophageal cancer with oral bisphosphonate use was raised from data from the FDA54 and the United Kingdom.55 However, other investigations from the United Kingdom56 and Denmark57 have not found any association between the development of esophageal cancer and oral bisphosphonate use. The FDA recently announced plans to continue review of the conflicting studies.58

### Markers of Bone Turnover

Monitoring markers of bone turnover such as NTX and bone-specific alkaline phosphatase (BALP) may be useful in assessing the extent of bone disease in patients with solid tumors metastatic to bone and multiple myeloma. NTX is released into the bloodstream and excreted in the urine during osteoclast-mediated bone resorption.28,30,59

A retrospective analysis from the phase III zoledronic acid trials in patients with solid tumors determined that the majority of patients with bone metastases from solid tumors had elevated urinary NTX levels compared with healthy young adults.59 Elevated NTX levels correlated with an increased risk for SREs and disease progression compared with low NTX levels. Moderate and high NTX levels were also associated with an increased risk of death compared with low levels. In addition, increased levels of BALP were related to an adverse outcome.59

Bone turnover markers may also reflect response to treatment. An analysis of patients with bone metastases from non–small cell lung cancer found that a decrease in urinary NTX levels was associated with a response to therapy as well as improvement in time to disease progression.25 An analysis of three large phase III trials of patients with solid tumors and bone metastases reported similar results, with 70% to 81% of zoledronic acid-treated patients with elevated NTX levels experiencing normalized NTX levels in the first 3 months. Normal NTX levels correlated with improved survival and response to therapy.56

One trial evaluated the effect of denosumab in patients with prostate, breast, or other cancers and bone metastases and elevated urinary NTX levels despite ongoing intravenous bisphosphonate therapy with pamidronate or zoledronic acid.61 Normal NTX levels were achieved for 71% of patients who received denosumab compared with 29% of patients who continued intravenous bisphosphonates (P < .001). The proportion of patients who maintained lower NTX levels at week 25 was higher for the denosumab group than for the intravenous bisphosphonate group (64% vs 37%; P = .01). The incidence of SREs also favored the denosumab group (8%) compared with the bisphosphonate group (17%). Future studies may provide evidence from markers of bone turnover to identify patients at high risk for bone metastases or bone lesion progression.

### Safety of Bone-Targeted Therapy

#### Bisphosphonates

Safety and efficacy data of intravenous bisphosphonates in the metastatic setting are predominantly limited to 24 months of treatment. The most frequently reported side effects from intravenous bisphosphonates are fever and myalgias, which may occur in up to 55% of patients, typically within 12 hours of the initial infusion. Anti-inflammatory agents may easily provide relief. Diarrhea and gastric irritation may develop with the oral bisphosphonates ibandronate and clodronate, which are not approved in the management of bone metastases in the United States. Electrolyte abnormalities, including hypophosphatemia, hypocalcemia, hypomagnesemia, and hypermagnesemia, are rarely reported with intravenous bisphosphonates. Other conditions such as vitamin D deficiency, hypoparathyroidism, hypomagnesemia, or use of medications such as interferon, aminoglycosides, or loop diuretics may provoke these abnormalities.18
Renal toxicity with an increase in creatinine levels from baseline may occur in approximately 10% of patients receiving zoledronic acid or pamidronate. The renal toxicity is related to the specific bisphosphonate, the dose schedule, the duration of administration, and concomitant medications. Creatinine clearance should be assessed prior to administration of intravenous bisphosphonates. Lowering the dose according to treatment guidelines and prolonging the infusion time may reduce this problem.18

Osteonecrosis of the jaw (ONJ) is an uncommon adverse event that occurs in 1.4% of patients receiving bisphosphonates.24 It usually develops after a dental procedure. Other risk factors for development of ONJ include glucocorticosteroids, preexisting dental or periodontal disease, and use of thalidomide. The appearance of an area of necrotic bone in the oral cavity in a patient who has not received radiation therapy to this area is a typical presentation of ONJ.18

The use of bisphosphonates in patients without cancer has not been conclusively associated with an increased risk for developing cancer. There is no evidence that the use of bisphosphonates increases the risk for a new primary tumor or disease progression in patients with cancer.18 On the contrary, findings support the anticancer benefits of zoledronic acid, which are discussed earlier in this review.

**Denosumab**

Gastrointestinal irritation has not been reported with denosumab, but an increased incidence of pancreatitis has been found with this drug.18 Transient hypocalcemia may occur more frequently with denosumab (5.5%) than with zoledronic acid (3.4%).24 Although renal toxicity may develop with denosumab, it is less common than with zoledronic acid (4.9% vs 8.5%, respectively; \( P = .001 \)).24 An increased risk of serious infections, including endocarditis, erysipelas, cellulitis, and infectious arthritis, has been reported with denosumab.18 Although ONJ is uncommon with denosumab, the phase III trials in the setting of bone metastases revealed similar or even higher rates of ONJ with denosumab than with zoledronic acid (2% vs 1.4%, respectively; \( P = .39 \)).24 Thus far, no adverse cancer outcomes have been reported in trials comparing denosumab with zoledronic acid.

**Guidelines for Bone-Targeted Therapy**

The American Society of Clinical Oncology (ASCO) first published evidence-based clinical practice guidelines for the use of bisphosphonates in breast cancer in 2000. These guidelines have been recently updated to include denosumab after its FDA approval and recommendations regarding ONJ. The guidelines stipulate that therapy with bone-modifying agents is recommended only for patients with evidence of bone destruction due to bone metastases from breast cancer.

The approved agents include denosumab (120 mg subcutaneously every 4 weeks), intravenous pamidronate (90 mg over no less than 2 hours), and zoledronic acid (4 mg over no less than 15 minutes every 3 to 4 weeks). There is insufficient evidence to demonstrate greater efficacy of one agent over another. No change in dosage, infusion time, or interval of administration is required for patients with a calculated creatinine clearance of more than 60 mL/min. Serum creatinine levels should be monitored before each dose. In patients with a creatinine clearance between 30 and 60 mL/min, a dose reduction detailed in the package insert for zoledronic acid should be used.62,63

The ASCO guidelines also recommend that all patients should receive a dental examination and appropriate preventive dentistry before therapy with bone-modifying agents is initiated and should maintain optimal oral health thereafter. Standards of care for management of bone pain from cancer should be employed in conjunction with therapy with bone-modifying agents. Furthermore, the use of biochemical markers to monitor these pharmacologic agents is not recommended. There are no contraindications to the use of calcium and vitamin D supplements.63 The National Comprehensive Cancer Network (NCCN) has also developed similar guidelines for the use of bisphosphonates and denosumab in patients with breast and prostate cancers and the use of bisphosphonates in patients with kidney cancer and multiple myeloma.64-67

Despite these excellent guidelines, several issues remain unresolved. Further research is needed to determine the optimal duration of treatment or treatment interval for patients who receive these medications for years. Additional data on risk profiles for developing serious adverse events from bone-modifying agents are also essential. The potential benefits and risks of initiation of these drugs prior to the development of bone destruction may also provide valuable insights.

**Economic Considerations**

Several retrospective health care resource utilization studies have found that the development of SREs confers a significant economic burden on the health care system. The average cost of treatment of an SRE has ranged from $9,480 to $13,940.68-71 Total medical care costs are also substantially higher, with means of $27,982 to $48,173 for a patient with clinically significant SREs vs no SREs.68-71

The benefits of bone-targeted agents in reducing the risk of SREs in a variety of solid tumors and multiple myeloma should be weighed against the costs of these drugs. A monthly dose of zoledronic acid currently costs approximately $844 compared with $1,650 for a monthly injection of denosumab.72 An editorial by West73 questioned whether the modest superiority of denosumab justifies the increased expense. However, the ease of subcutaneous injection and the lack of a need
to closely monitor creatinine levels may possibly offset the cost difference. On the other hand, a generic version of zoledronic acid, expected in early 2013, will offer a significantly less expensive but comparable alternative to the current agents. Further investigation into these aspects of health care is warranted.

**Ongoing Investigations and Future Directions**

New pharmacologic agents and pathways are under investigation for treatment of metastatic bone disease. Results are eagerly awaited from the phase III Southwest Oncology Group SO307 trial that compared three bisphosphonates — zoledronic acid, clodronate, and ibandronate — as adjuvant treatment in patients with breast cancer to delay or prevent bone metastases (NCT00127205).

Ssrc, a member of the membrane-associated nonreceptor tyrosine kinase family, is overexpressed in many cancers and plays an essential role in osteoclast activation and bone resorption.74 Dasatinib, an oral tyrosine kinase inhibitor that targets Src tyrosine kinase, has demonstrated antiosteoclastic activity in various models.17,74 Dasatinib is currently approved by the FDA for treatment of chronic myeloid leukemia. Two ongoing trials are evaluating the use of dasatinib either alone or in combination with zoledronic acid for patients with breast cancer metastatic to bone (NCT00566618 and NCT00410813).17,75

Another promising class of compounds is directed at the inhibition of cathepsin K, a lysosomal cysteine protease, which is selectively produced by osteoclasts. A phase II trial of odanacatib, a cathepsin K inhibitor, showed significant reduction in bone marker levels after 4 weeks of treatment in women with breast cancer bone metastasis.76 Cathepsin K inhibitors clearly harbor untapped potential for future clinical trials.

A novel approach to the prevention or treatment of bone metastases is the use of CXCR4 inhibitors. The chemokine receptor CXCR4 plays an integral role in bone metastases by magnetizing tumor cells to bone marrow and is highly expressed in the setting of bone metastases. CTCE-9908, a competitive antagonist of CXCR4, decreased the tumor burden of breast cancer in bone, other organs, and the primary breast tumor.77 A possible synergistic effect of the combination of CXCR4 and bisphosphonates has been suggested, but to date it has not been explored.

Transforming growth factor beta (TGF-β) is a prominent cytokine known to promote the invasion and metastasis of multiple cancers.78 An inhibitor of TGF-β receptor was shown to reduce the incidence of diffuse skeletal metastases in an experimental mouse model of breast cancer-induced bone metastasis.79 These are encouraging data, but the implications have yet to be studied in the clinical setting.

Another investigational approach is the inhibition of integrin receptors. Integrin acts by physically anchoring osteoclasts to the bone support matrix. A preclinical study using rat models demonstrated inhibition of integrin ß3, which measurably lowered osteoclast activity.80 All the aforementioned results of ongoing investigations are encouraging. Although further exploration is warranted, the results forecast the development of novel, improved, and potentially effective approaches to the treatment of bone metastases.

**Conclusions**

Bone metastases occur frequently in a variety of cancers. The development of this condition may cause a variety of serious consequences for patients, including fractures, pain, and the need for surgical and radiation therapy interventions. Effective systemic therapies for metastatic bone disease are available that reduce skeletal-related events. Ongoing and future research efforts in this field may provide additional encouraging options for treatment.

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