Prevention and Management of Bone Metastases in Lung Cancer

A Review

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Abstract: Approximately 30 to 40% of patients with advanced lung cancer will develop bone metastases in the course of their disease, resulting in a significant negative impact on both morbidity and survival. Skeletal complications of bone metastases include pain, pathologic fractures, spinal cord compression, and hypercalcemia. Total medical care costs are greater among patients with bone metastases who develop skeletal complications. A randomized phase III trial of the third generation bisphosphonate zoledronic acid has shown clinical benefit in the management of a subgroup of patients with bone metastases from lung cancer. Zoledronic acid treatment was associated with a reduction in both the risk of, and time to, a skeletal-related event. One of the markers of bone resorption, N-telopeptide, is both prognositic for development of skeletal-related events and predictive for benefit from zoledronic acid. In preclinical models, bisphosphonates have also demonstrated antitumor activity and are therefore currently being evaluated in adjuvant trials. Inhibition of the receptor activator of nuclear factor kappa B ligand-RANK pathway can reduce osteoclast-mediated bone resorption, and trials comparing receptor activator of nuclear factor kappa B ligand inhibitors with bisphosphonates are ongoing, including patients with lung cancer. In this article, we review the management of bone metastases and hypercalcemia as well as potential future directions for bone directed therapies in patients with lung cancer.

Key Words: Bone metastases, Lung cancer, Bisphosphonates.

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The incidence of bone metastases in advanced lung cancer patients is estimated to range from 30 to 40%.[1,2] Furthermore, at autopsy, lung was the primary site in more than 50% of cases in patients who presented with bone metastases and an occult primary.[3] In non-small cell lung cancer (NSCLC) in particular, a recent single-institution retrospective review of 435 patients with NSCLC revealed an incidence of 24% for skeletal metastases with the majority of those (66%) detected at the time of initial staging.[4] The axial skeleton and proximal long bones were the most commonly involved and approximately half of these patients required radiation therapy.

Bone metastases are seldom asymptomatic, and in 2.3% of lung cancer patients, symptoms of bone metastases are the first manifestation of malignancy.[5] In fact the most frequent form of pain reported in cancer patients is pain from skeletal metastases and 80% of lung cancer patients with bone metastases may suffer from bone pain either at presentation or some time during the course of their cancer.[4,6] Bone metastases frequently lead to skeletal morbidity that can result in a significant negative impact on both quality of life and survival; the median survival for patient with bone metastases is $<$6 months.[1]

Skeletal-related events (SREs) is a term used to describe a collection of adverse events associated with bone metastases that are collated to use as an end point in clinical trials. SREs include pathologic fractures, the requirement for surgery or radiotherapy, spinal cord and nerve root compression, and hypercalcemia of malignancy.[1] Patients who experience an initial SRE are at high risk for subsequent SREs.[7] These SREs result in impaired mobility, reduced quality of life, and frequently require therapeutic intervention (radiation therapy, surgery, and systemic treatments) that may add considerable cost to the end of life care. Indeed, a retrospective review from Japan reported a 30% incidence of skeletal metastases in patients with NSCLC, half of whom subsequently experienced an SRE.[8]

Mechanisms of Bone Metastases Development and Bone Destruction

Neoplastic involvement in the bone arises from dysregulation of the normal bone remodeling process, usually tightly controlled in balance between the bone resorption function of osteoclasts and the remodeling and bone formation mediated by osteoblasts.[9] The "vicious cycle" of bone metastases occurs when tumor cells stimulate osteoclast activity leading to bone resorption. The bone matrix then

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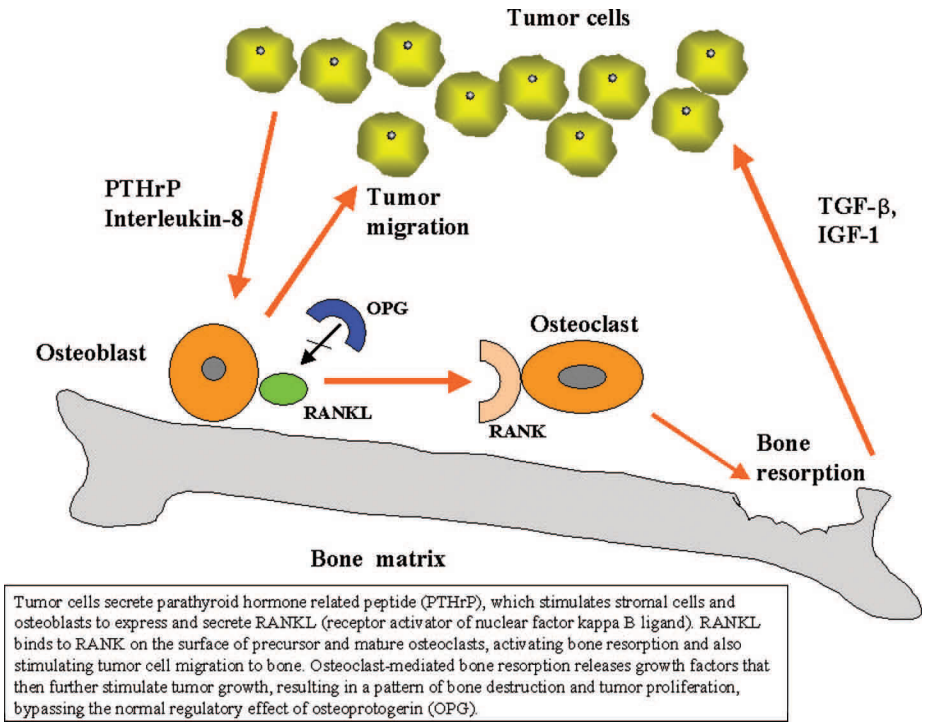

FIGURE 1. The vicious cycle of bone destruction and tumor proliferation.

releases cytokines that stimulate further tumor growth, hence creating a self-propagating circuit of tumor growth and bone destruction (Figure 1).

More specifically, tumor production of cytokines such as parathyroid-hormone-related peptide (PTHrP) and interleukin 8 stimulates osteolysis.[10–12] This mechanism works through the RANKL (receptor activator of nuclear factor kappa B ligand)/receptor activator of nuclear factor kappa (RANK)/OPG (osteoprotegerin) axis. RANKL, also known as osteoprotogerin ligand or tumor necrosis factor-related activation-induced cytokine, has been identified as a key mediator of osteoclast differentiation, function and survival.[13–15] RANKL is expressed on osteoblasts, both in transmembrane and soluble form, and when increased expression is stimulated by factors such as PTHrP or prostaglandins, RANKL binds to RANK receptors on osteoclast precursors, which in turn stimulates migration of cancer cells to the "fertile soil" of bone.[16] Maturation of osteoclast precursors to multinucleated osteoclasts and finally to activated osteoclasts is initiated on RANKL/RANK binding. Osteoclast-mediated bone resorption in turn causes release of growth factors, such as transforming growth factor-beta and insulin-like growth factor 1, that complete the cycle by stimulating further tumor growth.[17–19] RANKL is regulated by OPG, a member of the tumor necrosis factor receptor family that is normally present in bone marrow. OPG acts by binding to and inhibiting RANKL, thereby preventing the RANKL-RANK binding that stimulates osteoclast differentiation and maturation.[20] It is disruption of this RANK/RANKL/OPG axis that is key to progression of bone metastases.[16,21]

Although the overwhelming majority of lung cancer bone metastases are osteolytic in nature, case reports exist of osteoblastic bone metastases. Limited clinical evidence hypothesizes that these may have different etiology, and possibly are more common in patients with mutations of the epidermal growth factor receptor.[22]

In addition, in preclinical models, adhesion of cancer cells to the bone microenvironment have been shown to increase production of angiogenic factors (such as vascular endothelial growth factor) that enhance tumor growth in bone.[23] Clinical correlates of this mechanism have not yet been demonstrated in lung cancer. However, expression of bone sialoprotein in lung cancers, not usually seen in normal lung tissue, is strongly correlated with subsequent development of bone metastases and also seems to be an independent adverse prognostic factor.[24,25] This may be a useful potential target for future drug development. Finally, preclinical mouse models also have demonstrated up-regulation of the PTHrP and the ezrin genes in lung cancer bone metastases, potentially mediated by transforming growth factor-beta. Ezrin may be a potential target for future research.[26]

Economic Impact of Skeletal Complications

In a retrospective observational study using a large American health insurance claims database, Delea et al.[27] reported the high cost of treating SREs in lung cancer. SREs were defined as pathologic fractures, cord compression, hypercalcemia, bone surgery, radiotherapy, or initiation of opioid analgesic therapy (although initiation of opiates is not normally considered an SRE). Charges were compiled for out-patient procedures, hospital stays, doctor office visits, prescriptions, and home and long-term care. Patients with SREs were matched to similar patients without SREs by age and comorbidity scores using a propensity score approach. Of

534 patients identified with lung cancer and bone metastases, 295 (55%) experienced one or more SREs over a mean follow-up of 5.6 months, whereas 25% of patients had two or more SREs. After matching, there were 162 patients each in the SRE and non-SRE groups. Costs of treatment of SREs were estimated to be approximately $9500. Total medical care costs were almost $28,000 in patients with SREs and were significantly higher that in patients without SREs ($p < 0.001$). Radiation therapy accounted for 55% of the treatment cost (compared with 25% for bone surgery), and 54% of costs were due to in-patient hospitalization. The authors concluded that the costs of SREs in patients with lung cancer and bone metastases were substantial and potentially greater than previously estimated, thereby providing a rationale for treatment to prevent SREs.

Provisional data from the United Kingdom suggests that the use of zoledronic acid in lung cancer patients with bone metastases may be cost effective, with the mean drug cost (£1473) slightly lower than the cost of additional SREs (£1562) seen in an untreated population. However, this analysis was highly modeled and fully published details are not yet available.[28]

MANAGEMENT OF BONE METASTASES

Treatment of pain is one of the most important aspects in the management of bone metastases. Nonsteroidal antiinflammatory drugs can be used alone for mild pain from bone metastases and in conjunction with narcotic analgesics for more severe pain. Corticosteroids, tricyclic antidepressants, anticonvulsants, and neuroleptics have been all used in conjunction with opioids for improved pain control.[29]

Radiation therapy is the most common treatment for palliation of painful bone metastases, stabilization of impending pathologic fractures, and treatment or prevention of spinal cord compression. In a review of palliative therapy for lung cancer, Bezjak[30] observed that the dose fractionation used for the treatment of bone metastases varies widely from single fractions, usually in doses of 8 Gy, to short-course radiation of 20 to 30 Gy in 8 to 10 fractions, and even more radical treatment of up to 50 Gy. Reported pain relief response rates ranged from 65 to 100%, although the response criteria used in the studies varied widely. A recent guideline from the Supportive Care Guidelines Group of Cancer Care Ontario recommended the following: "Where the treatment objective is pain relief, a single 8 Gy treatment, prescribed to the appropriate target volume, is recommended as the standard dose-fractionation schedule for the treatment of symptomatic and uncomplicated bone metastases."[31] This guideline is supported by the results of two meta-analyses of radiotherapy dose-fractionation trials that found no relation with either dose or fractionation scheme in the palliation of bone metastases in multiple tumor types including lung cancer.[32,33] Interestingly, however, the former meta-analysis showed that the need for retreatment was significantly higher in patients treated with only a single fraction ($p = 0.002$).[32] Clearly, not all patients are suitable for single fraction therapy.

A recent review of the factors influencing the use of single versus multiple fractions of radiotherapy for bone metastases at the Princess Margaret Hospital, Toronto showed that out of 882 courses of radiation, only 283 (32%) were delivered as a single fraction.[34] Patients given single fractions tended to be older, to have a history of weight loss, and to be of poorer performance status. The study included 358 patients with lung cancer, but there was no difference in selection of dose or fractionation by tumor type. These clinical factors, particularly short-life expectancy and poor performance status, may guide clinicians toward treatment with a single fraction if it is felt that the need for retreatment would be unlikely.

Surgical intervention is a mainstay of treatment for pathologic fractures and prevention of impending fractures when long weight-bearing bones are involved.[35] Surgery is considered in spinal cord compression but is usually limited to cases where there is spinal instability, failure of conservative management, progressive neurologic deterioration from bony collapse, or intractable pain.[36,37] Although very uncommon, there are a few case reports that have showed long-term survival in patients with lung cancer and solitary bone metastases treated with aggressive surgical resection of the both primary and metastatic sites of disease.[38,39]

Bisphosphonates for Bone Metastases

Bisphosphonates are a group of compounds that are stable analogues of naturally occurring inorganic pyrophosphate. When bound to hydroxyapatite, they are specific inhibitors of osteoclast activity and this subsequently leads to inhibition of bone resorption.[40–42] The most commonly investigated bisphosphonates in cancer are the first-generation compound clodronate (Bonefos; Schering AG, Berlin, Germany), second-generation pamidronate (Aredia; Novartis Pharmaceuticals Corporation, East Hanover, NJ), third-generation zoledronic acid (Zometa; Novartis Pharma Stein AG, Stein, Switzerland), and third-generation ibandronate (Boniva; Roche Laboratories Inc., Nutley, NJ).

In addition to the effect on osteoclasts, in a preclinical model Reinholz et al.[43] demonstrated that the bisphosphonates pamidronate and zoledronate decreased osteoblast proliferation and stimulated their differentiation and bone-forming activity. In addition, bisphosphonates have direct effects on cancer cells by inhibiting tumor cell invasion and adhesion to bone matrix, and in human breast cancer and prostate cancer cell lines they have been shown to inhibit growth and induce apoptosis.[44–46]

Bisphosphonates are effective therapy for the hypercalcemia of malignancy, relief of malignant bone pain and delay of the onset of progressive bone disease. The majority of studies evaluating the use of bisphosphonates have been in bone metastases from breast cancer, multiple myeloma, and prostate cancer. Phase III trials, comparing pamidronate versus placebo in breast cancer patients with bone metastases, demonstrated a significant reduction in the number of SREs, time to first SRE, pain scores, and use of analgesia for those receiving pamidronate.[47,48] Similar benefits were seen in multiple myeloma, with a reduction in SREs seen after nine cycles of pamidronate compared with placebo,[49] an effect that was maintained with long term use up to 21 cycles of

pamidronate.[50] Zoledronic acid, a highly potent third-generation nitrogen containing bisphosphonate, has shown similar efficacy to pamidronate in phase III trials for patients with both breast cancer and multiple myeloma.[51,52] Zoledronic acid is administered as a 15-minute intravenous infusion when compared with a 90-minute infusion for pamidronate. In patients with metastatic breast cancer, it has been favored over pamidronate in a multiple-event analysis. Here, zoledronic acid was found to further reduce the risk of an SRE and benefits were maintained over a long follow-up period, in addition to the convenience of a shorter infusion time.[53]

In prostate cancer, where bone metastases are predominantly osteoblastic, pamidronate has not been shown to reduce bone pain or the rate of SREs when compared with placebo.[54] In contrast, zoledronic acid did significantly reduce the rate of SREs in metastatic prostate cancer when compared with placebo.[55] Zoledronic acid has therefore demonstrated efficacy in both osteolytic and osteoblastic bone disease.[56]

The most common adverse events associated with bisphosphonate administration include bone pain, fever, anemia, and gastrointestinal disturbances. All bisphosphonates should be used with caution in patients with risk factors for renal dysfunction. Rarer side effects such as osteonecrosis of the jaw have gained considerable attention in breast cancer and myeloma management, although only isolated cases have been reported in lung cancer.[57]

Bisphosphonates have also demonstrated antitumor activity based on preclinical evidence in both in vitro and in vivo studies, including in lung cancer cell lines.[58,59] Recently, in a large phase III trial of adjuvant hormonal therapy in early stage breast cancer, patients were randomized to receive zoledronic acid or not. Provisional results have shown a significant reduction in the risk of disease free survival events (hazard ratio [HR] = 0.64 [0.46, 0.91]; $p = 0.01$) and a trend toward improvement in overall survival (HR = 0.60 [0.32, 1.11]; $p = 0.10$), favoring zoledronic acid.[60] Based on these observations, there may also be a rationale for further trials in patients with early and advanced stage lung cancer, for prevention of bone metastases and a possible survival advantage.

Bisphosphonates for Bone Metastases from Lung Cancer

Rosen et al.[61] conducted a multicenter phase III, double-blind, randomized clinical trial comparing zoledronic acid and placebo in 773 patients with bone metastases from lung cancer and solid tumors other than breast and prostate cancer. Patients were randomized to receive zoledronic acid (4 mg or 8 mg) or placebo every 3 weeks for 9 months, and patients were then given the option to continue blinded treatment for a total of 21 months. Because of concerns regarding renal safety at the higher dose, a protocol amendment led to the 8-mg dose being reduced to 4 mg. Most of the patients in this group had already completed therapy, but 25% had their treatment reduced to the lower dose. All patients received calcium and vitamin D supplements. The primary end point was the proportion of patients with ≥1 SREs at 9 or 21 months. Secondary end points were the time to first SRE, annual incidence of SREs, multiple-event analysis, pain/analgesic scores, bone lesion response, time to progression of the disease, and safety (including survival). Hypercalcemia was included as secondary efficacy analysis for the definition of SREs.

Of the 773 patients, 378 had NSCLC and 58 had small cell lung cancer. Twenty-five percent of patients completed the 9-month core and 101 patients elected to continue in the extension phase of study. Compared with placebo, treatment with 4 mg of zoledronic acid resulted in a nonsignificant reduction in the proportion of patients with an SRE (38 versus 44%; $p = 0.127$). However, when hypercalcemia was included in analysis of skeletal events, zoledronic acid significantly reduced the proportion of patients with an SRE (38 versus 47%; $p = 0.039$) (Table 1). Zoledronic acid significantly extended the median time for the development of SRE (including hypercalcemia) by almost 3 months (230 days versus 155 days; $p = 0.007$) and the time to first pathologic fracture (238 days versus 161 days; $p = 0.031$). Furthermore, in multiple-event analysis a 27% reduction in the risk of developing an SRE (including hypercalcemia) was observed (HR = 0.70, $p = 0.006$), a finding that was similar in the subset containing only lung cancer patients (HR = 0.71, $p = 0.036$).

TABLE 1. Comparison of Zoledronic Acid 4 mg vs. Placebo in Solid Tumors

	Zoledronic Acid (4 mg)	Placebo	*p*
Overall number of patients	257	250	
Lung cancer patients	141	139	
Skeletal-related event outcomes for all patients			
Proportion with one SRE within 9 mo	38%	44%	0.13
Any skeletal-related event (including hypercalcemia)	38%	47%	0.04
Radiation to bone	27%	32%	
Pathological fracture	16%	21%	
Spinal cord compression	3%	4%	
Hypercalcemia	0%	3%	0.004
Time to first SRE (including HCM)	230 d	155 d	0.01
Time to first pathological fracture	238 d	161 d	0.03
Skeletal-related event outcomes for NSCLC patients			
Proportion with one SRE within 9 mo	42%	45%	0.56
Time to first SRE	171 d	151 d	0.19
Hazard ratio of occurrence of SREs in lung cancer patients (NSCLC + SCLC)			
SRE (not including hypercalcemia)	0.73	1	0.61
SRE (including hypercalcemia)	0.71	1	0.04
Survival outcomes for all patients			
Median time to disease progression	89 d	84 d	0.12
Median overall survival	203 d	183 d	0.62

Data from Rosen et al.[61]

SRE, skeletal-related event; HCM, hypercalcemia of malignancy; NSCLC, non-small cell lung cancers; SCLC, small cell lung cancers.

TABLE 2. Biomarkers in a NSCLC Patient Subset of a Study of Zoledronic Acid 4 mg vs. Placebo in Solid Tumors, Demonstrating Elevated NTX is Prognostic for SREs and Predictive of Benefit from Zoledronic Acid

	Zoledronic Acid	Placebo	*p*
N-telopeptide			
Number of patients with high-baseline NTX	102/183 (56%)	42/80 (53%)	
Relative risk of SRE if high-baseline NTX (reference to normal baseline NTX)	1.81	1.64	
	$p = 0.01$	$p = 0.07$	
Relative risk of death (95% CI) if normal baseline NTX	1.33 (0.84–2.09)	1	0.22
Relative risk of death (95% CI) if high-baseline NTX	0.65 (0.45–0.95)	1	0.025
NTX and bone-specific alkaline phosphatase			
Relative risk of death if high-baseline BALP	Not stated	1	0.40
Relative risk of death if high-baseline BALP and high NTX	0.54	1	0.006
Relative risk of death if low-baseline BALP and high NTX			NS

Data from Hirsh et al.[63] and Brown et al.[64]
SRE, skeletal-related event; NTX, N-telopeptide; BALP, bone specific alkaline phosphatase.

Biochemical markers of bone resorption (N-telopeptide [NTX] and deoxypyridinoline) decreased significantly from baseline with zoledronic acid, 4 mg. There was no significant difference in survival and global quality of life parameters between the groups. Zoledronic acid at a dose of 4 mg was found to be safe and well tolerated, with the most common reported adverse events being bone pain, nausea, anemia, and emesis. Renal impairment was higher in the zoledronic acid group when this was administered as a 5-minute infusion, but after a protocol amendment changed the infusion time to 15 minutes there was no significant difference in renal impairment between treatment and placebo groups.

The authors subsequently reported a long-term follow-up of the same cohort of patients.[62] At 21 months, the main study findings were confirmed, where patients treated in the 4 mg cohort had a 31% reduction in the risk of skeletal complications compared with placebo (HR = 0.69, 95% confidence interval 0.54–0.89, $p = 0.003$). However, the primary end point, the number of patients with an SRE at 21 months, still did not reach statistical significance (39 versus 46%, $p = 0.127$). In view of the poor prognosis for this patient population, who had a median survival of 6 months, only a minority of patients completed the study (approximately 25%). However, this was the first trial to show clinical benefit of bisphosphonate therapy in patients with bone metastases associated with solid tumors other than breast and prostate cancer.

More recently a retrospective analysis, of only the NSCLC patients from this study, correlated high-baseline levels of NTX with an increased risk of SREs in both the zoledronic acid and placebo groups. Among 144 patients with a high-baseline NTX, treatment with zoledronic acid significantly reduced the risk of death (HR = 0.65, $p = 0.025$), in addition to a reduction in SREs seen across all patients (relative risk 0.62, $p < 0.001$).[63] A further analysis of the same subgroup of patients investigated the influence of bone-specific alkaline phosphatase (BALP). Although zoledronic acid was not predictive of improved survival in patients with elevated baseline BALP, in patients with both elevated NTX and elevated BALP treatment with zoledronic acid was associated with a 46% reduction in risk of death ($p = 0.006$) when compared with placebo[64] (Table 2).

Although we are not aware of other randomized studies of zoledronic acid in lung cancer yet reported, there is more evidence to support its use. In a retrospective analysis of a US claims database, zoledronic-acid-treated lung cancer patients with bone metastases had a 30 to 40% reduced risk of skeletal complications when compared with untreated patients.[65] There are no randomized trials of other bisphosphonates in the treatment of skeletal complication from solid tumors other than breast or prostate cancer. In a single arm phase II study, pamidronate was administered to 20 patients (16 NSCLC and 4 small cell lung cancer) with bone pain because of lung cancer metastases.[66] Pain relief was achieved in 12 patients (60%) and normalization of serum calcium was seen in all nine patients with hypercalcemia.

Ibandronate is a third-generation bisphosphonate that is available in both intravenous and oral formulations. In a feasibility study, 4 mg ibandronate was safely infused over 20 minutes in 32 patients with bone metastases. There was a significant decrease in serum calcium levels ($p = 0.03$) and 24 patients stabilized or reduced their need for analgesic treatment.[67] Ibandronate has been compared with pamidronate in patients with bone metastases from breast or lung cancer.[68] Although this study only included 25 patients (10 with lung cancer), the authors concluded that ibandronate seemed superior to pamidronate in alleviating pain, improving motility, improving overall quality of life, and reducing bone resorption in patients with bone metastases from these two malignancies. A Chinese phase IV trial (NCT00492843) has recently been terminated because of poor accrual. It was aiming to assess the efficacy and safety of a loading dose versus standard dose of intravenous ibandronate in reducing pain in patients with lung cancer and bone metastases. This is based on several open-label trials that suggest that intravenous ibandronate administered on consecutive days can provide rapid relief from severe or opioid-resistant metastatic bone pain of various primary tumors.[69,70]

Finally, in a retrospective study evaluating 94 patients who received radiation for bone metastases from either breast cancer or NSCLC, 27 patients (12 with NSCLC) also received clodronate, an oral bisphosphonate. Pain measures (increase in pain on the first day of radiation and complete pain relief after radiation) were better in the group that received clodronate compared with those treated with radiotherapy alone.[71]

For the future, a phase III trial in Europe is currently evaluating the safety and efficacy of zoledronic acid in the prevention or delaying of bone metastases in patients with stage IIIA and IIIB NSCLC. This trial is open and actively recruiting participants (clinicaltrials.gov identifier NCT00172042). The US75 trial (Z-PACT, NCT00086268) is an open label, multicenter phase III study evaluating the effect of zoledronic acid in combination with chemotherapy (carboplatin and docetaxel) in patients with stage IIIB/IV NSCLC not metastatic to bone. This study has completed accrual and results are awaited. A phase II study of zoledronic acid in lung cancer patients with bone metastases is currently recruiting, with the primary outcome measure being change in tartrate resistant acid phosphatase—5b levels. This study will help to define the role of markers of bone resorption in this group of patients (NCT00265200).

Targeting RANK Ligand

Denosumab (AMG142, Amgen Inc., Thousand Oaks, CA), a fully humanized monoclonal antibody with high affinity and specificity for RANKL, can bind and neutralize the activity of human RANKL. This action, that is similar to the action of native OPG, has been shown to result in inhibition of osteoclast function and bone resorption.[72] A phase II study in 255 women with breast cancer-related bone metastases evaluated five different doses of subcutaneously administered denosumab and one cohort treated with intravenous bisphosphonates (91% received zoledronic acid). All five denosumab arms showed marked biologic activity in suppressing bone turnover and reducing SREs, which was similar to bisphosphonate arm.[73] In the above study and others, denosumab has been generally well tolerated; the most common adverse events reported were fatigue, nausea, headache, bone pain, and upper respiratory tract infection. Larger phase III trials are underway to investigate the effect of denosumab compared with zoledronic acid for prevention and treatment of complications caused by bone metastases in patients with advanced cancer (including lung cancer). The selected dose was 120 mg subcutaneously every 4 weeks based on favorable efficacy, safety, and pharmacokinetic profile.

MANAGEMENT OF HYPERCALCEMIA

Hypercalcemia of malignancy is a fairly common and life-threatening skeletal complication of bone metastases associated with lung cancer. A prospective study in the 1970s of 200 patients with lung cancer showed a 12.5% incidence of hypercalcemia.[74] Squamous cell carcinoma is the most common histology associated with this presentation, generally in advanced-stage disease,[75] although hypercalcemia is occasionally reported in small cell lung cancer as well.[76] Although hypercalcemia may occur with osteolytic bone metastases, it is often seen in the absence of osseous involvement because of humoral and cytokine factors such as PTHrP, interleukin-1, transforming growth factor alpha, tumor necrosis factor, prostaglandin, and lymphotoxin.[77] PTHrP stimulates bone resorption and renal phosphate wasting by working through a common receptor for PTHrP and parathyroid hormone, resulting in hypercalcemia and hypophosphatemia. PTHrP frequently can be detected in the serum of patients with humoral hypercalcemia of malignancy.[78]

Clinical symptoms of hypercalcemia depend on the serum calcium level and the rate of rise. Early symptoms include nausea and vomiting, fatigue, anorexia, muscle weakness, constipation, polyuria, nocturia, and polydypsia. If untreated patients can become severely dehydrated and subsequently develop renal impairment. Further effects include confusion, psychosis, seizure, coma, arrhythmia, pruritis, and ileus. The goals of treatment include vigorous rehydration, inhibition of bone resorption and/or promotion of calcium excretion, and treatment of the underlying malignancy.[79]

The bisphosphonates are the most commonly used drugs used in the management of the hypercalcemia of malignancy, including lung cancer. In a pooled analysis of two randomized trials comparing zoledronic acid with pamidronate for patients with hypercalcemia, a higher complete response rate was seen in those treated with 4 mg zoledronic acid (88 versus 70%, $p = 0.002$).[80] As discussed earlier, in the study by Rosen et al.[61] (zoledronic acid versus placebo in lung cancer and other solid tumor patients with bone metastases) hypercalcemia was completely prevented in the 4 mg zoledronic acid arm.

FUTURE DIRECTIONS

All studies of treatment for bone metastases have used different end points to assess response, including degree of pain relief, need for narcotic analgesics, development of hypercalcemia and development of pathologic fractures to name but a few. Furthermore, timing of these assessments has varied from study to study from 1 month to almost 2 years. Clearly a 2-year end point would be of little relevance in advanced lung cancer patients, whereas it might be totally appropriate in prostate and breast cancer patients. Chow et al.[81] have published an international consensus statement that recommends a uniform set of criteria for the selection of outcome measures and the timing of assessments in radiotherapy trials for bone metastases. Many of the recommendations may also be applicable to medical trials for bone metastases. In addition, the European Organization for the Research and Treatment of Cancer is developing a bone metastasis quality of life module that may also help to standardize symptomatic response to therapy and evaluate the quality of life effects that bone metastases have on cancer patients.[82]

Another limitation to clinical research strategies to evaluate therapies for bone metastases are the limitations of current radiologic techniques.[83] There has, therefore, been significant impetus to develop biochemical surrogates of bone

function. Biochemical markers of bone metabolism are associated with both the formation and destruction of bone. Bone resorption markers include NTX, tartrate resistant acid phosphatase—5b, pyridinoline, and deoxypyridinoline, whereas BALP is a bone formation marker. Elevated levels of these markers have been identified in the serum and urine of patients with bone metastases. They may provide early indication of bone metastases and may be elevated even in patients without radiologic evidence of metastatic bone disease.[84] High-baseline levels of urinary NTX have been shown to be a strong prognostic indicator of negative outcome in several cancers including lung cancer, with increased risk of SREs, disease progression, and death compared with patients with low-NTX levels.[63,85,86] Therefore, measurement of biochemical markers of bone turnover may be useful to monitor the extent of bone metastases and the overall response to therapy in the future. An interesting example of this biochemical analysis has been in the targeting of RANK ligand with denosumab, where osteoclast inhibition correlated with reduced urinary NTX levels and a reduction in SREs.[73]

CONCLUSION

Bone metastases from lung cancer are associated with considerable negative effects on both patient morbidity and mortality. Total medical care costs of SREs are significant among patients with bone metastases from lung cancer. Zoledronic acid is the first and only bisphosphonate that has proven efficacy for the treatment of bone metastases from a broad range of solid tumor types, including lung cancer, and should be strongly considered for such patients. Future and ongoing trials will assess the role of bisphosphanates in the adjuvant setting and assess the efficacy of RANKL antibodies. Use of biomarkers may further identify subgroups of patients most likely to benefit from bisphosphonates and perhaps other treatments.

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