ABSTRACT

Approximately 30% to 40% of patients who succumb to lung cancer will ultimately be diagnosed with bone metastases, and the majority of these individuals will be symptomatic because of bony involvement. This article offers a discussion on the mechanisms of bone metastases in lung cancer, with a focus on the association between clinical events and biochemical markers. Elevated levels of certain markers, such as N-telopeptide and bone-specific alkaline phosphatase, have been tied to increased risks of skeletal-related events, progression of bone disease, and death in patients with bone metastases, irrespective of tumor type. This article also includes a review of symptomatology, including the incidence of asymptomatic versus symptomatic bone metastases in lung cancer and the most commonly presenting symptoms. In a study examining the incidence of skeletal metastases in relation to symptoms in patients with non-small-cell lung cancer, investigators found that in 42% of these individuals, the signs and symptoms of bone metastases were the presenting factors that led to evaluation and diagnosis of the malignancy. Of patients with bone metastases, 80% had localized bone pain at presentation or at a later time. Also provided in this article is an extensive discussion of the incidence and impact of skeletal-related events on quality of life, healthcare costs, and survival time in patients with various malignancies, including lung cancer.

Osteolytic and osteoblastic lesions, whereas prostate carcinoma and multiple myeloma are usually associated with the development of osteoblastic lesions and osteolytic lesions, respectively. Several factors contribute to the pathogenesis and progression of bone metastasis, including various growth factors, parathyroid-related protein, tumor necrosis factor, and prostaglandins. These factors are associated with diverse pathologic mechanisms that regulate bone metastases, including early vascular dissemination of cancer cells, adhesion of cancer cells to the bone microvasculature and matrix components, chemotaxis and proliferation of cancer cells in the bone, osteolysis by tumor cells, stimulation of tumor-associated macrophages and osteoclasts, and tumor-induced local osteoblastic proliferation.

**USE OF BIOCHEMICAL MARKERS IN ASSESSING BONE METASTASES**

Several markers of bone metabolism are associated with bone destruction and bone formation. Elevated levels of these markers have been identified in the serum and urine of patients with bone metastases, and some of these markers can be used to predict clinical events in bone metastases. One study examined the prognostic implications of specific markers of bone resorption (cross-linked N-telopeptide [NTX], pyridinoline cross-linked peptides, and deoxypyridinoline cross-linked peptides) and bone formation (bone-specific alkaline phosphatase) on skeletal-related events (SREs), bone disease progression, and death in patients with various malignancies. Data were extracted from several clinical trials evaluating zoledronic acid and pamidronate in bone metastases associated with various malignancies. Patients were categorized based on their most recent marker measurements (low, moderate, or high) at the time of the event. Researchers found a strong correlation between any elevation in levels of NTX and an increased risk of SREs, progression of bone disease, and death in patients with bone metastases, irrespective of tumor type. These events were also linked with elevated levels of alkaline phosphatase. Researchers concluded that routine measurement of NTX could be a potentially important clinical tool in assessing patients’ risk of developing SREs.

While examining the effects of intervention on bone markers, researchers found that zoledronic acid (4 mg) immediately and consistently reduced urinary levels of NTX, pyridinoline, and deoxypyridinoline in patients with solid tumors. Zoledronic acid was also found to slightly reduce serum levels of bone alkaline phosphatase. Taking the data one step further, a retrospective analysis evaluated the effects of zoledronic acid on survival in patients with metastatic lung cancer and high levels of NTX or high levels of both NTX and bone alkaline phosphatase. Compared with placebo, zoledronic acid was found to reduce the relative risk of death by 35% and 46%, respectively. However, in patients who had high baseline NTX and normal bone alkaline phosphatase levels, the relative risk of death was similar between zoledronic acid and placebo groups.

**SIGNS AND SYMPTOMS OF BONE METASTASES**

Of the patients with lung cancer who develop bone metastases, 30% to 60% are initially asymptomatic, underdiagnosed, and undertreated, as evidenced by a study indicating that close to 40% of lung cancer patients with bone metastases are “falsely” negative at initial staging. Symptomatic bone metastases from bronchogenic cancer occur in greater than one third of patients with late-stage non–small-cell lung cancer (NSCLC) and is associated with poor prognosis. A recently published retrospective review of 371 patients with NSCLC examined the incidence of skeletal metastases in relation to symptoms. Investigators found that approximately 25% (n = 87) of patients had skeletal metastases, and in 42% of these individuals, the signs and symptoms of bone metastases were the presenting factors that led to evaluation and diagnosis of NSCLC. Therefore, bone metastases were the first manifestation of metastatic disease in these patients. The vast majority of metastases were found in the spine (thoracic and lumbar regions), ribs, sacrum, iliac, and, to a lesser extent, the femur, cervical spine, skull, and the humerus scapula sternum. Of the patients with bone metastases, 80% had localized bone pain at presentation or at a later point when lesions grew symptomatic or first manifested. Other symptoms included compression/pathologic fracture, hypercalcemia, cord compression, nerve impingement, radicular pain, extremity paresthesias or weakness, and bladder incontinence.

Bone scan has historically been the standard tool used to diagnose bone metastases, but it has fallen out of favor because of a high rate of false positivity in the
setting of trauma or degenerative joint disease and false negativity in myeloma. Positron emission tomography (PET) scan is more sensitive and more specific, but it may miss disease below the mid femurs, depending on how far the PET scan is extended. Confirmatory imaging is useful in identifying large or lytic lesions and blastic disease, but it frequently misses more subtle lesions. Magnetic resonance imaging (MRI) is particularly useful in identifying metastases in the spine, shoulder, hips, and pelvis. Computed tomography imaging with bone windows is used in patients who cannot undergo an MRI.

**RECOGNITION OF SKELETAL-RELATED EVENTS**

Bone metastases cause considerable morbidity, placing patients at risk for SREs, including severe pain, impaired mobility, symptoms of hypercalcemia, pathologic fractures, spinal cord compression, and bone marrow infiltration (more commonly seen in myeloma and small-cell lung cancer). These SREs lead to functional impairment/loss of autonomy, rapid deterioration in quality of life, increased medical costs, and a negative effect on survival. Bone pain, the most common symptom associated with metastases, is experienced by more than 80% of patients with bone involvement, and is often the first indication that the tumor has metastasized to the bone.

Pain is often sharp, intermittent, and becomes worse at night. Over time, achiness becomes progressive, continual, and is exacerbated by weight-bearing activity or any use of bone or musculoskeletal structure. Patients with bone metastases will frequently graduate from nonsteroidal anti-inflammatory drugs to narcotics fairly quickly. Pain has a detrimental impact on patients’ quality of life, interfering with daily activities and limiting patients’ capabilities. As a result, patients often have feelings of anger, fear, and depression.

Clinical trials have shown that at least 1 SRE occurs in as many as 45% of patients with bone metastases. In patients who do experience an SRE, average survival time is a dismal 4 months. Some tumors, such as those that occur in the breast, are associated with 2 to 3 SREs yearly in those with bone metastases. Studies have shown that SREs often occur in clusters; therefore, patients with at least 1 SRE are at high risk for subsequent SREs. Although SREs vary somewhat by tumor type, the most common SREs include pain, radiation to bone, and pathologic fractures.

Skeletal complications negatively impact patients’ quality of life by hindering their ability to perform basic functions. Recently, an analysis was undertaken to examine the acute effects of SREs on quality of life in patients with prostate cancer and bone metastases who had experienced at least 1 SRE during a large clinical trial. Investigators observed significant declines in physical, functional, and emotional well-being.

SREs also have a negative impact on survival time. The precise reason for this association is unclear, but the presence of bone lesions often occurs concomitantly with metastases to soft tissue. Also, metastases to visceral sites eventually lead to organ failure and death, and are, therefore, associated with impaired survival. More recent research indicates that the overall survival of patients with prostate cancer and a history of skeletal fractures is reduced, compared with patients who do not have skeletal fractures. It is also conceivable that SREs may accelerate a decline in function and performance status, hastening death.

Based on several recent studies conducted in the Netherlands, healthcare costs associated with SREs are substantial. Results from one of these studies in patients with metastatic prostate cancer found that the average total cost of treatment was €1053 per patient over the 24-month follow-up period, which included an average cost of €6975 euros per patient for treatment of SREs. In this population, more than 50% of the treatment costs were directly associated with the management of SREs. Similarly, significant costs directly related to treating SREs were observed among patients with breast cancer and multiple myeloma. Average treatment costs for managing metastatic breast cancer patients ranged from €7364 to €19680, with costs directly related to treating SREs ranging from 6% to 20% of the treatment costs. In multiple myeloma, average treatment costs ranged from €19754 to €37218, with 13.4% to 21% of the treatment costs attributable to SREs.

A recent study of patients with lung cancer quantified the incidence of SREs in lung cancer, evaluated the costs of SREs in patients with bone metastases, and evaluated the burden of SREs. Researchers found that 55% of lung cancer patients with bone metastases experienced 1 or more SREs over a mean follow-up of 7.4 months; 20% of patients had 2 or more events. Total cost of treatment was approximately $22,000 greater in patients with SREs, compared with those without SREs. Main cost drivers were radiotherapy
CONCLUSIONS

Bone metastases are associated with considerable morbidity and a poor overall prognosis in all oncology patients. These consequences can be further compounded by late diagnosis, which is common because 30% to 60% of patients with lung cancer who develop bone metastases are asymptomatic, and therefore, are undiagnosed and undertreated. Patients with bone metastases are often at risk for SREs (eg, severe pain, impaired mobility, hypercalcemia, and pathologic fractures), which contribute to functional impairment/loss of autonomy, rapid deterioration in quality of life, increased medical costs, and a negative effect on survival. In an effort to ameliorate this devastating complication of malignancy, considerable research is being conducted on the pathogenesis of bone metastases. For example, certain biochemical markers have been identified in association with bone formation and destruction. These are being used to predict clinical events and are used as possible therapeutic targets. Research milestones such as these offer promise for investigators and clinicians who are trying to reduce the burden of bone metastases in lung cancer and other malignancies.

DISCUSSION

Dr Ettinger: I agree that the PET scan, which is now routinely used in staging for NSCLC, has replaced the bone scan in detecting bone metastases. What about a case of isolated bone metastasis that is PET positive? What would be your next step to confirm bone metastasis: the plain film, and if that is negative, go to MRI? If the MRI is negative, proceed to biopsy? Or do you treat it?

Dr Langer: That sequence is appropriate, but it depends on the site and who is reading the PET or bone scan. Assume a solitary rib lesion that appeared semi-innocent was PET positive. We have often seen such a lesion on bone scan, and we see it just as well, if not better, with PET. Many of those patients have nonmetastatic involvement, so we start with a plain film. Or, we will ask the patient if there is a history of trauma to that region. In bone scan, the appearance may be different. If it is solitary and round, it is frequently traumatic; if more linear, then it is often metastatic. With other sites, I often go straight to MRI, eliminating the plain film, which, more often than not, is equivocal or nondiagnostic.

Frequently, when you evaluate a plain film, there is still uncertainty. I find that the MRI is probably the ultimate arbiter. Only rarely have we had to perform a biopsy. We will biopsy the lesion if we are still unsure and if it portends a critical difference between the palliative and curative approach.

Dr Curran: I agree. Particularly in the pelvis and spine, if you are looking at a subtle lesion on PET or bone scan, MRI is what you must use. If you suspect multiple lesions, plain film can be helpful.

Dr Brahmer: Often, you will have an older woman who has had osteoporotic fractures. It can be difficult outside of the PET and bone scan to tell exactly what it is, and it can even be difficult with an MRI.

Dr Curran: This is particularly an issue with breast cancer. There are competing risks for new onset severe pain and a vertebral event between the osteoporosis of the postmenopausal woman and the metastatic disease. There are circumstances in which the diagnosis is not as clear as it should be, and the management has to be carefully delineated. Imaging can be helpful, but you are really distinguishing one type of abnormality from another in that example.

Dr Langer: There is an unpublished phenomenon. NSCLC patients who have had combined modality for local NSCLC can acquire thoracic spinal abnormalities. Typically, it is characterized by fairly abrupt onset pain, but not always; the presentation is akin to non-neoplastic compression fractures. Usually, we will request an MRI or alternative imaging and the radiologist will say there is metastatic involvement. Only with time is the true nature of these abnormalities elucidated. I think there is a real risk for vertebral insufficiency fractures in patients who have received combined chemoradiation therapy, particularly for locally advanced NSCLC.

Dr Curran: I was not aware of that. In the early days of breast tangent radiotherapy, it was made clear that rib fractures in the tangent field that occurred years later were a rare, but predictable, effect of radiotherapy. If there has been prior radiotherapy, you must alert the radiologists. They understand the marrow differences between an irritated versus a nonirradiated...
vertebral body so that there will not be a misinterpre-
tation of marrow involvement by disease as well.

Dr Ettinger: How do you envision bone scan use in
the future? It may ultimately be of historical inter-
est only.

Dr Langer: I think there is still potential for its
use. In situations where I have obtained bone scan and
PET scan results, they have often corroborated each
other.

Dr Ettinger: One problem today is that many
patients have had multiple scans, even before their first
consultation.

Dr Langer: This bone scan/PET scan issue has not
been adequately communicated to the internal medi-
cine world, certainly not beyond oncology.

Dr Brahmer: How do you think that the bio-
markers for bone involvement will be used to manage
patient care?

Dr Langer: We must investigate biomarkers fur-
ther in the context of prospective studies. We need to
examine any study seeking to determine whether zole-
дроникуш одьо (or any compound) can prevent or delay
done metastases. If these preliminary observations are
verified, then it may become a useful management
tool. I am not sure whether it will change for patients
who already have established bone metastases and who
are already on some type of intervention. On the other
hand, it might permit us to fine-tune our therapy. For
example, if we knew of a specific dose or dose range
that was associated with better suppression of urinary
NTX levels, or other factors, this might translate into
better outcome; then maybe routine biomarker studies
would have some utility. We do not have that infor-
mation now.

Dr Berenson: There is some data indicating that
patients with better suppression of these biomarkers are
less likely to have SREs. A study is beginning now for
breast cancer patients with documented bone meta-
tases. Projected accrual is 1400 patients and the study
will compare oral ibandronate and intravenous zole-
дроникуш одьо. The study will be looking at dosing based
on baseline NTX less than 50. There is 1 group that
will be treated monthly, and the other group will be
based on NTX of 50, 50 to 100, or greater than 100;
patients less than 50 will receive less frequent dosing.

Dr Ettinger: There is pathologic material that is
being retrospectively examined for bone sialoprotein.
There is an increased risk of bone metastasis with ele-
vated bone sialoprotein. You are correct that patients
with breast cancer, prostate cancer, and myeloma live
longer than patients with lung cancer. However, patients
with lung cancer are starting to live longer as a result of the newer therapies. If you could identify a
marker that predicts the patient will have a significant
risk of bone metastasis, maybe you could then use a
bisphosphonate to try to prevent it.

There is a study that I proposed in the Eastern
Cooperative Oncology Group (ECOG) and it is still
in the ECOG Symptom Management Committee: to
look at stage IV NSCLC disease and randomize
between bisphosphonate (zoledronic acid) versus
placebo to see if we could prevent or delay the onset of
bone metastasis.

Dr Berenson: There is a large German-Italian joint
study that is ongoing and looking at patients without
stage IV, stage IIIA, or stage IIIB, to determine
whether metastasis can be prevented.

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