Therapeutic Potential of Denosumab in Patients With Lung Cancer: Beyond Prevention of Skeletal Complications

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Abstract

Approximately up to 40% of patients with lung cancer develop bone metastasis, with 22% to 59% of them experiencing skeletal-related events (SREs), which result in an important quality of life deterioration and economic burden. Denosumab, a fully human antibody that targets the receptor activator of nuclear factor-κB (RANK) ligand (RANKL), is indicated for prevention of SREs in patients with solid tumors and has demonstrated superiority in breast and prostate cancer, and in other solid tumors, in reducing the risk of first SRE by 17% versus zoledronic acid. In the subset of patients with non–small-cell lung carcinoma (NSCLC), denosumab has also shown a positive trend to SRE risk reduction. Denosumab might have direct or indirect antitumor effects. Cancer cells produce factors that stimulate increased bone resorption by osteoclasts, which in turn release tumor growth factors into the bone microenvironment, initiating a tumor/bone vicious cycle. An increasing body of evidence suggests RANK/RANKL signaling plays a role in this tumorigenesis. Both proteins are overexpressed in different tumor types including lung cancer cells. RANK/RANKL signaling activates nuclear factor-κB pathways related to lung carcinogenesis and increases intercellular adhesion molecule 1 expression and MEK/extracellular signal-regulated kinase phosphorylation, which in turn enhances tumor cell migration. In animal NSCLC models, denosumab delayed bone metastases and reduced skeletal tumor growth. In patients with lung cancer (post hoc analysis), denosumab prolonged overall survival by 1.2 months versus zoledronic acid ($P = .01$). This hypothesis-generating outcome warrants further investigation and 2 studies in lung cancer are ongoing to elucidate the therapeutic potential of denosumab beyond SRE prevention.

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Introduction: Burden of Bone Metastases and Skeletal Complications in Lung Cancer

Lung cancer is one of the most frequent cancers, and accounts for approximately 20% of cancer mortality.[1] Non–small-cell lung cancer (NSCLC) is the most frequent type of lung cancer (85%).[2]

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Currently, 1- and 5-year survival rates remain at approximately 45% and 12% of patients, respectively.[3,4] In Europe, the incidence and 5-year prevalence of lung cancer in 2012 were 410,220 and 442,810 individuals, respectively,[1] of whom 71% were male. Overall, the annual age-standardized mortality rate was 24.0 per 100,000.[1] In Spain, the incidence and 5-year prevalence were 26,711 and 28,148 individuals, respectively.[1] The 3-year survival rate is approximately 13%.[5]

Because of the unspecific symptomatology of early disease, most cases of NSCLC are diagnosed at an advanced stage (78%),[6] with bone being one of the most frequent sites of metastasis. The incidence of bone metastases in the course of the disease ranges between 30% and 40%,[7,8] and approximately 65% of cases are found at diagnosis. The presence of bone metastases is related to a reduced survival (median overall survival of 6-12 months[7,9]): multiple bone lesions, high bone turnover marker levels, and history of pathological fractures are also associated with a shorter survival.[10]

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Bone metastases in lung cancer are characterized mainly by severe pain and lytic nature.[11,12] Many asymptomatic bone lesions are not diagnosed in clinical practice.[8] Positron emission tomography (PET) scans are the most common method of diagnosis,[13] and have a greater sensitivity than computed tomography (CT) scans.[14] If PET is not available, bone scintigraphy might be also useful. Current guidelines recommend performing a CT scan of the chest and upper abdomen at diagnosis of NSCLC for tumor staging.[15] If bone metastases are clinically suspected, bone imaging is required. In addition to PET and CT for systemic screening, magnetic resonance imaging is recommended to describe a localized bone metastasis. For distant metastasis assessment, fluorodeoxyglucose–PET-CT scan offers the highest sensitivity.[15]

As a consequence of an impaired bone turnover, an important proportion of patients with bone metastases experience skeletal-related events (SREs).[16-18] SREs are defined as the presence of pathologic fracture, radiation to bone, spinal cord compression, or surgery to bone, and are a serious complication. In a 21-month study, the incidence of SREs in lung cancer patients with bone metastases who did not receive bone-targeted agents ranged from 40% in patients without a history of SREs (median of 209 days to first SRE) to 52% in patients with previous SREs (median of 106 days).[16] Another study in a large US population reported that SREs were present in 22% of lung cancer patients at diagnosis of bone metastasis, with a cumulative incidence of 59%.[19]

Because of the need for surgery and lengthy hospitalizations in most cases,[20] these events have devastating consequences for the quality of life of late-stage cancer patients.[21] Most skeletal complications also cause a decrease in the ability to perform the basic functions of daily living, and have an effect on mortality.[22-24]

The costs of managing patients with bone metastasis from lung cancer who suffer SREs are much higher than those without a SRE.[25] In the United States, the estimated lifetime SRE-related cost per lung cancer patient is $11,979, being mainly explained (61%) by radiotherapy cost.[26] In a European study in lung cancer patients with at least 1 SRE, 41% of the events required hospitalization during a median of 19 days.[27] In several studies from Germany,[28] Spain,[28,29] Italy,[28] the United Kingdom,[28] Portugal,[30] and Belgium,[31] costs of each SRE were in the following ranges: pathologic fractures: €4712 to €8730; radiation to bone, €1485 to €3877; spinal cord compression: €7903 to €13,203; and surgery to bone: €3348 to €12,092. In a French study of 554 lung cancer patients with bone metastasis, 49.5% of yearly costs related to bone metastasis could be assigned to SREs.[32]

Antiresorptive drugs, including denosumab and bisphosphonates, are recommended for prevention of SREs in patients with lung cancer and bone metastasis.[33-35]

Because bone metastases represent an important problem for the patient and health system, their prevention and treatment are key in the management of lung cancer. Denosumab is a bone-targeted agent for treatment of metastatic bone disease. Herein, we review the available evidence on its efficacy in preventing skeletal complications in lung cancer patients with bone metastasis, and also the increasing body of evidence that supports a potential direct antitumor effect of denosumab.

Current Management of Bone Metastasis in Lung Cancer

Zoledronic acid, the most effective bisphosphonate, has been historically considered the standard of care for the prevention of skeletal complications in patients with bone metastasis from lung cancer. In a phase III study (n = 773), zoledronic acid significantly delayed the median time to first SRE (236 vs. 155 days; $P = .009$) and reduced the risk of a SRE by 31% versus placebo (hazard ratio [HR], 0.69; 95% confidence interval [CI], 0.54-0.88; $P = .003$, multiple event analysis).[18] Although the trial was only powered for the primary end point, a subset analysis in the NSCLC subgroup found a trend toward a longer time to first SRE (median 171 vs. 151 days; $P = .188$) and a 27% reduction in the risk of SREs in favor of 4 mg zoledronic acid (HR, 0.73; 95% CI, 0.52-1.02; $P = .061$) versus the placebo group.[36] An important limitation for zoledronic acid use is the potential nephrotoxicity, which could be increased by the comorbidities commonly associated with lung cancer, older age and tobacco use, and by the platinum-based chemotherapy. Cisplatin-based regimens are a common treatment option in patients with bone metastases, and are associated with dose-dependent nephrotoxicity.[37] Zoledronic acid therapy must be accompanied by renal monitoring and requires dose adjustments in patients with renal insufficiency, which might lead to suboptimal efficacy.[38] In lung cancer, up to 23% of patients have creatinine clearance (CrCl) < 60 mL/min.[39] Zoledronic acid is contraindicated in patients with CrCl < 30 mL/min, and must be reduced from 4.0 to 3.5 mg in patients with a CrCl between 60 and 50 mL/min, to 3.3 mg in those with a CrCl between 50 and 40 mL/min, and to 3.0 mg in those whose CrCl is within 40 to 30 mL/min.[40] Renal adverse effects lead to withdrawals in many cases (17% and 9%, respectively[41]). Globally, only between 15%[42] and 34%[43] of patients with bone metastases from lung cancer receive intravenous (I.V.) bisphosphonates in the United States, and only 1 in 10 receive them in a preventive way (ie, before a SRE) (5% vs. 10% for primary vs. secondary prophylaxis).[42]

Denosumab in the Prevention of Skeletal Complications

Denosumab is a fully human monoclonal antibody (immunoglobulin [Ig] G2) that targets and binds with high affinity and specificity to the receptor activator of nuclear factor-κB (RANK) ligand (RANKL), mimicking the natural action of osteoprotegerin (OPG), an endogenous RANKL inhibitor.[44] RANK is a member of the tumor necrosis factor (TNF) receptor superfamily.[45] Activation of RANK by the RANKL promotes the maturation of preosteoclasts into osteoclasts.[46] In metastatic bone disease, tumor cells secrete factors that increase the expression of RANKL, upregulating osteoclast activity which, in turn, releases growth factors from the bone matrix that might perpetuate tumor activity.[47,48] Denosumab prevents the RANK/RANKL interaction from occurring, which inhibits the formation, function, and survival of activated osteoclasts and blocks the vicious cycle of bone destruction and tumor growth (Figure 1).[46-48]

Denosumab has been approved globally for prevention of SREs in patients with solid tumors.[44,49] The recommended dose for prevention of SREs in adults with bone metastasis from solid tumors is 120 mg administered as a single subcutaneous injection