Effect of Bisphosphonates, Denosumab, and Radioisotopes on Bone Pain and Quality of Life in Patients with Non–Small Cell Lung Cancer and Bone Metastases: A Systematic Review

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ABSTRACT

Bone metastases are common in patients with non–small cell lung cancer (NSCLC), often causing pain and a decrease in quality of life (QoL). The effect of bone-targeted agents is evaluated by reduction in skeletal-related events in which neither pain nor QoL are included. Radioisotopes can be administered for more diffuse bone pain that is not eligible for palliative radiotherapy. The evidence that bone-targeted agents relieve pain or improve QoL is not solid. We performed a systematic review of the effect of bone-targeted agents on pain and QoL in patients with NSCLC. Our systematic literature search included original articles or abstracts reporting on bisphosphonates, denosumab, or radioisotopes or combinations thereof in patients with bone metastases (≥5 patients with NSCLC), with pain, QoL, or both serving as the primary or secondary end point. Of the twenty-five eligible studies, 13 examined bisphosphonates (one also examined denosumab) and 12 dealt with radioisotopes. None of the randomized studies on bisphosphonates or denosumab evaluated pain and QoL as the primary end point. In the single-arm studies of bisphosphonates a decrease in pain or analgesic consumption was found for 38% to 77% of patients. QoL was included in five of 13 studies, but improvement was found in only two. No high-level evidence that bisphosphonates or denosumab reduce pain or improve QoL was found. Although the data are limited, radioisotopes seem to reduce pain with a rapid onset of action and duration of response of 1 to 3 months. The evidence that bisphosphonates or denosumab reduce or prevent pain in patients with NSCLC and bone metastases or that they have an influence on QoL is very weak. Radioisotopes can be used to reduce diffuse pain, although there is no high-level evidence supporting such use.

Keywords: Non–small cell lung cancer; Bone metastases; Bone-targeted agents; Pain; Quality of life

Introduction

Bone metastases develop in approximately 30% to 40% of patients with non–small cell lung cancer (NSCLC) during the course of their disease, and in more than 60% of such patients skeletal lesions are found at primary diagnosis.[1–3] To prevent or delay the occurrence of skeletal-related events (SREs), zoledronic acid, denosumab, or both are usually advised in guidelines. This advice is based on studies that include not just patients with NSCLC.[4–7] SREs are defined as occult or symptomatic pathological fractures or both, spinal cord

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compression, palliative radiotherapy, and sometimes also hypercalcemia of malignancy (HCM). This composite measurement was developed for and used as the primary end point in studies evaluating pharmacological therapies aimed at bone metastases.[8–10] Pain and quality of life (QoL) are not included in the definition of SRE. Bone pain is known to be an important issue in patients with NSCLC inasmuch as approximately 70% of patients with the disease require opioids and their pain often results in a decrease in QoL.[11,12] In a Cochrane review (2002) it was concluded that "there is evidence to support the effectiveness of bisphosphonates in providing some pain relief for bone metastases, but there is no sufficient evidence for effectiveness in different primary neoplasms." The review included only one lung cancer study, and it was published in Chinese only.[13] Since then, reviews have focused mainly on breast and prostate cancer. In two separate Cochrane systematic reviews, one on bone metastases in breast cancer and one on bone metastases in prostate cancer, a significant decrease in pain (breast) and a trend toward a decrease in pain (prostate) were found.[14,15] For lung cancer, not much data exist. One systematic review (published in 2011 and including only controlled trials) evaluated the efficacy of bisphosphonates (not restricted to zoledronic acid) for prevention of SRE, control of pain, and improvement of overall survival.[16] Pain reduction with zoledronic acid was evaluated in only one study: no significant pain reduction was found when zoledronic acid was compared with ibandronate.[16] In another review (two versions published in 2011, one as a summary of the other) that included only randomized controlled trials (RCTs), it was concluded that there are no adequate RCTs evaluating the effect of bisphosphonates or denosumab on bone pain and QoL in patients with NSCLC.[17,18] Denosumab was recently registered for the prevention of SREs in patients with solid tumors and bone metastases. For pain relief, radioisotopes are another option.[19–22]

Although pain and QoL are important issues in treatment of NSCLC with bone metastases, there are no RCTs and almost no controlled trials evaluating the effect of bisphosphonates, denosumab, or radioisotopes on pain relief and QoL in patients with NSCLC specifically. In this systematic review we assess the available evidence on the effect of these agents on bone pain and QoL in patients with NSCLC.

Methods

Search Strategy and Selection Criteria

A systematic search of the literature published between 1990 and January 2015 was performed using the PubMed, Medline, Embase, Web of Science, and Cochrane databases. The literature search was performed by following the patient, intervention, comparator, and outcome method,[23] which is shown in the appendix. The search terms were as follows: *NSCLC, non–small cell lung cancer, bone metastases, bone neoplasm, bisphosphonates, zoledronic acid, radionuclide, strontium, samarium, rhenium, radioisotopes, radioactive-labeled bisphosphonates, bone-targeted agents, denosumab,* and *rank ligand*.

Study Selection

After identification and exclusion of duplicates, two authors (L.H. and B.H.) independently screened the titles and subsequently the abstracts. The same two authors examined the full texts of selected articles with regard to the eligibility criteria. The articles reviewed had to report on bisphosphonates, denosumab, radioisotopes, or combinations thereof in a population of adults with cancer in whom bone metastases had been diagnosed; include at least five patients with NSCLC; and be written in English, German, or Dutch. Only original articles and conference proceedings were included; reviews were excluded. We chose to include studies irrespective of their epidemiological design because the reviews of Lopez-Olivo et al. and Ford et al. made it clear that there are almost no controlled clinical trials evaluating this topic that have been written in a language other than Chinese.[16,18] All inclusion and exclusion criteria are summarized in Table 1. To complete the search and

Table 1. Criteria for Inclusion in the Review

Criterion	Definition
Subjects included	Human only
Language	English, German, or Dutch
Article type	Original article or conference proceeding; reviews excluded
Number of patients	≥5 patients with NSCLC[a]
Site of primary tumor	NSCLC[a]
Tumor stage	IV, with bone metastases
Age	≥18 y
Treatment	Zoledronic acid, denosumab, radioisotopes, or some combination thereof; alone or combined with other treatments (e.g., chemotherapy)
Follow-up period	No lower or upper limit
Dosing, route, and frequency or duration of treatment	No restrictions
Outcome	Pain, QoL, or both as primary or secondary end point; all methods for pain measurement or QoL measurement allowed

[a]When type of "lung cancer" was not specified as NSCLC or SCLC, at least five patients with lung cancer patients had to be included.
NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; QoL, quality of life.