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STATE OF THE ART: CONCISE REVIEW

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.

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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.

identify all relevant studies, the references of all eligible articles were manually searched for additional potentially relevant studies.

Data Extraction

When available, the following data were extracted from eligible studies by one researcher (L.H.) and independently by another researcher (B.H.): year of publication; type of study (retrospective or prospective, phase, number of centers, study duration, and follow-up); total number of patients included and number of patients with NSCLC; type of intervention (type, dose, duration, route, and frequency of administration of bisphosphonates, denosumab, or radioisotopes or combinations thereof); comparator (placebo or another pain management drug); pain and QoL as primary or secondary outcomes; method and frequency of measurement of pain and QoL; and results.

Results

Selected Articles

The initial search yielded 1577 articles. After removal of duplicates and screening of titles, 104 abstracts were identified. On the basis of those abstracts, 27 articles or conference proceedings were selected for evaluation on a full-text basis.

On the basis of the inclusion and exclusion criteria, 18 full publications and two conference proceedings were deemed eligible for inclusion in this review. A manual search of the reference lists of the included articles identified five additional relevant articles (see the flowchart in Fig. 1).

Study Characteristics

Table 2 (bisphosphonates and denosumab) and Table 3 (radioisotopes) show the design of the studies included and summarize the comparison groups within

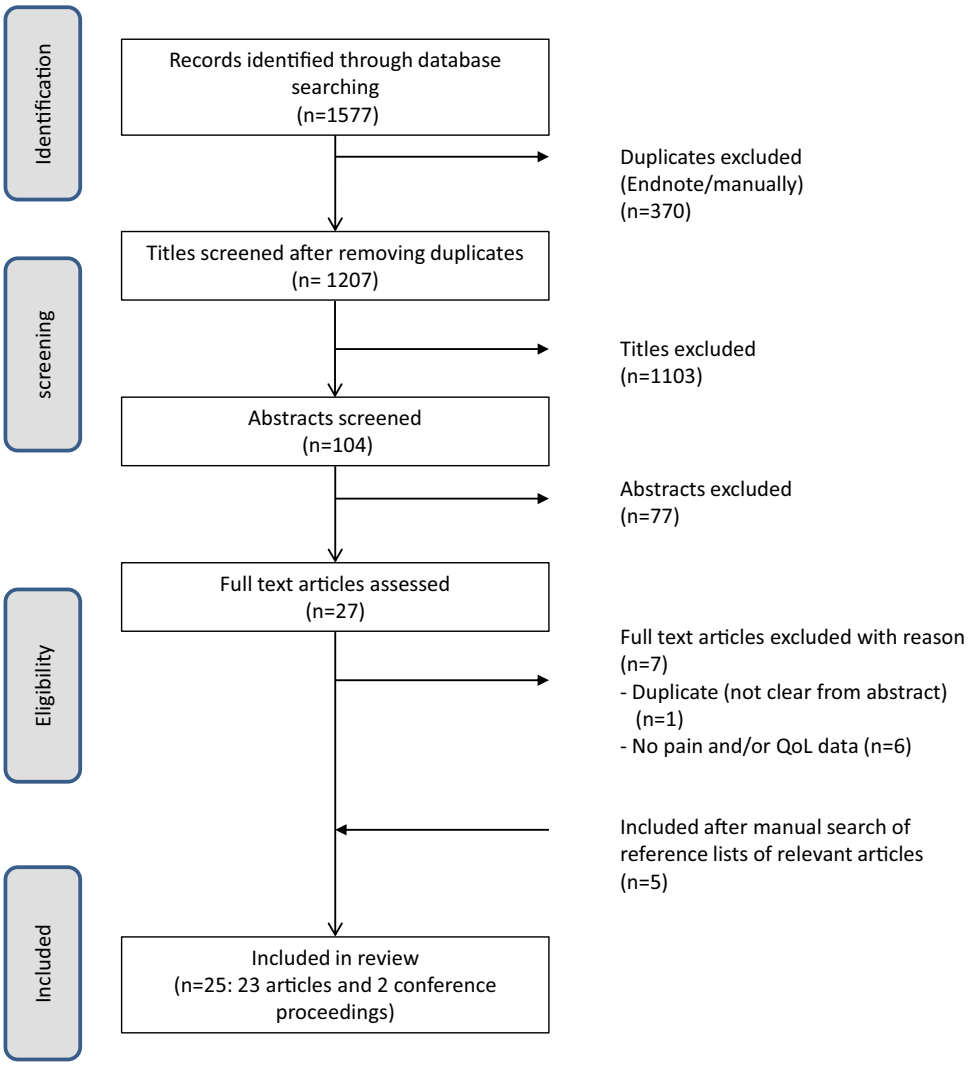

Figure 1. Flowchart for article selection.

Table 2. Characteristics of Trials Examining Bisphosphonates and Denosumab

Trial, y	Trial Type	Total Patients/ Patients with NSCLC	Treatment Arm	Comparator Arm	Follow-Up	Primary Study Objective	Secondary Study Objectives	Method and Frequency of Pain Measurement
Bisphosphonates								
Piga, 1998	Phase not mentioned, randomized, double blind, placebo controlled; number of centers and time period unclear	50/17	Clodronate, 1600 mg/d orally for 1 y, chemotherapy when necessary	Placebo, orally for 1 y	"at least 3 mo"	Symptom control, bone metastases; evolution measured by bone scan and radiograph	None	Pain (measured by VAS scale) and analgesic consumption, both monthly
Rosen, 2003; Update follow-up: Rosen, 2004	Phase III, randomized, double blind, placebo controlled, multicenter; time period unclear	773/378	CT with ZOL, 8/4 mg every 3 wk IV	CT with placebo every 3 wk	9-mo update: 21 mo	Proportion of patients with on-study SRE at 9 mo	Time to on-study SRE, including HCM; time to first SRE; skeletal morbidity rate; multiple-event analysis; pain score; analgesic use; ECOG PS; best bone lesion response; PFS; bone lesions; OS; bone markers; QoL	BPI, every 6 wk; analgesic score every 6 wk; FACT-G, frequency unclear
Kiaga, 2006	Phase not mentioned, single arm, single center, 2000–2001	32/32	CT with IBA, 4 mg by rapid infusion (20 min) every 3–4 wk IV until PD in bone	None	Mean 14 mo	Safety and efficacy	None	Changes in analgesic treatment, every visit (i.e., every 3–4 wk)
Facchini, 2007	Phase not mentioned, single arm, single center, time period unknown	60/28	CT with ZOL, 4 mg every 3–4 wk, 12 cycles	None	Not specified	Pain control, QoL	Safety, SRE	BPI; analgesic consumption through the narcotic score; FACT-G, frequency not mentioned
Kotteas, 2008	Phase not mentioned, single arm, single center, 2004–2005	86/74 (others SCLC)	CT with ZOL, 4 mg every 3–4 wk until PS deterioration or unacceptable toxicity	None	Mean 18 mo	Safety and efficacy	None	Changes in analgesic treatment, every visit (i.e., every 3–4 wk)
Longo (abstract only), 2008	Retrospective, centers unclear, 2007–2008	24/18 (others with SCLC)	CT with ZOL, 4 mg every 4 wk, cycles unknown	None	Not specified	SRE	Bone turnover markers, pain, QoL	BPI, EORTC QLQ-C30, frequency not mentioned
Zarogoulidis, 2009	Phase not mentioned, prospective, 2 arms (on basis of bone pain), number of centers unknown, years unknown	144/144	Patients with bone pain: CT with ZOL, every 4 wk after finishing CT, every 3 wk IV	Patients with no bone pain: docetaxel, 100 mg/m^2 plus carboplatin, AUC 6/every 4 wk (up to 8 cycles)	Unclear	OS, PFS, pain	None	VAS, each clinical visit

(continued)

Table 2. Continued

Trial, y	Trial Type	Total Patients/ Patients with NSCLC	Treatment Arm	Comparator Arm	Follow-Up	Primary Study Objective	Secondary Study Objectives	Method and Frequency of Pain Measurement
Francini, 2010	Phase not mentioned, prospective, randomized, blinding unknown, centers unknown, 2005–2010	55/55	CT with ZOL, 4 mg every 4 wk IV	CT every 4 wk, IBA 50, mg/d orally	3 mo	Effect of ZOL/IBA on bone turnover markers	Tumor response (RECIST), pain, SRE	6-Point intensity scale (McGill-Melzach), at baseline and at 1 and 3 mo
Ishiwata, 2011	Phase II, 2 arms, (control arm: patients who refused to enter study), 2 centers, 2007–2009	35/35	CT with ZOL, 4 mg IV every 4 wk (4–6 cycles)	Carboplatin (AUC = 6) every 4 wk with paclitaxel (70 mg/m^2) every wk or Nedaplatin (90 mg/m^2) every 4 wk with paclitaxel (70 mg/m^2) every wk (4–6 cycles)	9 mo	Feasibility of combination of CT with ZOL	QoL, SRE, toxicity, pain	Lung Cancer Symptom scale, every 4 wk, QOL-ACD
Del Signore, 2012 (abstract only)	Retrospective, centers unknown, 2007–2010	135/135	CT with ZOL, 4 mg every 4 wk	None	Not specified	Time to first and second SRE	Pain, QoL	VAS each clinical visit, EORTC QLQ-C30
Yoh, 2012	Phase not mentioned, single arm, centers unknown, 2007–2009	35/35	CT with ZOL, 4 mg every 3–4 wk , 4 cycles, ZOL continued afterward until unacceptable toxicity	None	Not specified	Feasibility of combination of CT with ZOL	Toxicity, SRE, pain score, best objective response, OS	BPI baseline and after 6 wk
Davidov, 2013	Phase not mentioned, open label, single arm, single center, 2004–2008	53/53	ZOL, 4 mg with CT, (gemcitabine 1250 mg/m^2 d1,8 and cisplatin 80 mg/m^2 d1, every 3–4 wk), number of cycles not specified	None	Not specified	Serum calcium and AF values	SRE pain	"Changes in analgesic treatment" not otherwise specified
Denosumab vs bisphosphonates								
Henry, 2014	Phase III, randomized, double blind, active comparator, multicenter study, 2006–2009	1597/702	Denosumab, 120 mg SC every 4 wk; placebo IV every 4 wk	ZOL 4, mg IV every 4 wk; placebo SC every 4 wk	7 mo	Time to first on-study SRE, time to first and subsequent SREs	OS, PFS, pain, analgesic use, AE	11-point BPI-SF, BPI-SF for pain interference in daily life, analgesic use: AQA, frequency: not mentioned

NSCLC, non-small cell lung cancer; VAS, Visual Analogue Scale; CT, chemotherapy; ZOL, zoledronic acid; IV, intravenously; HCM, hypercalcemia of malignancy; BPI, Brief Pain Inventory; FACT-GT, Functional Assessment of Cancer Therapy-General; IBA, ibandronate; PD, progressive disease; QoL, quality of life; SRE, skeletal-related event; AUC, area under the curve; RECIST, response evaluation in solid tumors; ECOG, Eastern Cooperative Oncology Group; OS, overall survival; PFS, progression-free survival; AF, alkaline phosphatase; TKI, tyrosine kinase inhibitor; SCLC, small cell lung cancer; PS, performance score; QOL-ACD, Quality of Life Questionnaire for Cancer Patients Treated with Anticancer Drugs; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire; SC, subcutaneously; AE, adverse event; BPI-SF, Brief Pain Inventory-Short Form; AQA, analgesic quantification algorithm.

Table 3. Characteristics of the Trials Examining Radioisotopes

Trial, y	Trial Type	Total Patients/ Patients with NSCLC	Treatment Arm	Comparator Arm	Follow-Up	Primary Study Objective	Secondary Study Objectives	Method and Frequency of Pain and QoL Measurement
Farhangi, 1992	Phase I, single arm, single center, time period and number of centers unknown	22/5	Sm-153-EDTMP in escalating doses, 3.7-37 MBq/kg, single dose IV, repeated if necessary in follow-up	None	Unclear	Pharmacokinetics, toxicity, pain response	None	VAS 3 times/d
Alberts, 1997	Composite of three phase I-II trials, number of centers unclear, 3-y period, number of years unknown	82/9 ("lung cancer")	Sm-153-EDTMP, 27.8, 55.5, or 111 MBq/kg IV, 1 dose, when necessary repeated after 6-8 wk (up to 4 doses)	None	Unclear	Efficacy and toxicity of different doses	None	VAS, frequency not mentioned
Kasalicky, 1998	Prospective, phase not mentioned, number of centers not clear, study period 3 y, number of years not clear	118/31 ("lung cancer")	^{89}SRCl, 150 MBq single dose IV, repeated if necessary in follow-up, but not within 3 mo	None	Unclear	Evaluation of palliative effect, toxicity	None	Analgesic consumption, composite pain score, improvement in KPS; changes in mobility, frequency not mentioned
Serafini, 1998	Phase III, randomized, double blind, placebo controlled, multicenter 1992-1994	118/6 ("lung cancer")	A: Sm-153-EDTMP, 18.5 MBq/kg; B: Sm-153-EDTMP, 37 MBq/kg	Placebo[b]	16 wk	Change from baseline AUC pain and 6-point pain score at wk 4 as the primary efficacy end point	Change in opioid use	Patient diary: - Daily VAS for each of 13 body regions combined into overall pain score according to methods of Donaldson, resulting in AUC for consecutive 7-d periods - Analgesic consumption, daily PGA: at every clinical visit (wk 1,2,3,4,8,12,16) 6-point pain score
Tian, 1999	Phase not mentioned, 2 arm, randomized,[a] single blind (patient), multicenter, start? - 1997	105/41 ("lung cancer")	Sm-153-EDTMP, 37 MBq/kg single dose IV	Sm-153-EDTMP, 18.5 MBq/kg single dose iv	Unclear	Toxicity and pain reduction	None	Patient diary of analgesic consumption, calculation of "sum of effect product" (on basis of pain score and time after Sm-153-EDTMP, the higher the SEP, the better the effect; weekly for first month, every 2 wk for second month, and every month thereafter
Küçük, 2000	Phase not mentioned, single arm, center and time not clear	31/5	RE-186-HEDP, 1295 MBq single dose IV, if necessary every 3 mo	None	Unclear	Efficacy and toxicity	None	Surrogate: improvement in ECOG and KPS, frequency not clear
Li, 2001	Phase II, single arm, centers and time period unknown	61/26 ("lung cancer")	RE-188-HEDP, 1-4 times IV, mean dose 1158 MBq	None	1 y	Efficacy	None	3-point pain scale

(continued)

Table 3. Continued

Trial, y	Trial Type	Total Patients/ Patients with NSCLC	Treatment Arm	Comparator Arm	Follow-Up	Primary Study Objective	Secondary Study Objectives	Method and Frequency of Pain and QoL Measurement
Li, 2002	Phase not mentioned, single arm, centers and time period unknown	66/20 ("lung cancer")	Sm-153-EDTMP, 740 MBq single dose IV	None	Unclear	Relationship between bone uptake of Sm-153-EDTMP and therapeutic effect	None	Composite score: CR: disappearance of >2 bone metastases, KPS: increase >20, moderate or complete relief of pain within 7 d of injection NR: no disappearance or shrinkage of metastases, KPS increase <10, no/slight remission of pain PR: all other patients
Zhang, 2003	Phase not mentioned, single arm, centers and time period unknown	30/25 (others SCLC)	RE-188-HEDP, mean dose 1158 MBq IV, when neccessary another dose at 1-1.5 mo	none	unclear	Efficacy	Not specified	4-point pain scale weekly, also pain diary
Leondi, 2004	Phase not mentioned, single arm, centers and time period unknown	24/18 (others SCLC)	RE-186-HEDP, 1295 MBq iv once	None	8 wk	Therapeutic efficacy RE-186 HEDP	None	VAS weekly, evaluation of analgesic consumption weekly, evaluation of QoL (surrogate: sleep duration, mobility, mood, daily activities) weekly
Minutoli, 2006	Phase not mentioned, single arm, single center, time period unknown	41/17	RE-186-HEDP, 1295 MBq IV, once, another dose when necessary	None	≥3 mo	Efficacy and toxicity	None	Pain index based on intensity, frequency, and number of involved skeletal segments, 1st mo weekly, every 2 wk thereafter
Cheng, 2011	Phase I, single arm, centers unknown, time period unknown	64/8	RE-188-HEDP, 20 to 50 MBq/kg	None	8 wk	Toxicity, pain reduction	None	VAS weekly, also pain diary

[a]Doctor or family could refuse lower dose of Sm-153-EDTMP.
[b]Treatment unblinded for patients who did not respond by wk 4, those who had received placebo could be given Sm-153-EDTMP, 1.0 mCi/kg, in an open manner.
NSCLC, non-small cell lung cancer; QoL: quality of life; EDTMP, ethylenediaminetetra(methylene phosphonate); HEDP, 1-hydroxy ethylidene-1,1-diphosphonic acid; IV, intravenously; VAS, Visual Analogue Scale; KPS, Karnofsky performance score; ECOG, Eastern Cooperative Oncology Group; AUC, area under the curve; SEP, sum of effect product; PGA: Physician Global Assessment; CR, complete response; NR, no response; PR, partial response.

each study. Because only one study examining denosumab with zoledronic acid as an active comparator was found, it was grouped within the table and results related to bisphosphonates.

Bisphosphonates and Denosumab

Thirteen studies (two of which were abstracts only) were found, with one study concerning both denosumab and bisphosphonates.[24–37] The update of the study of Rosen et al. was not counted as an extra study; rather, its results were documented and combined with the original 2003 study.[34,35]

Included Patients. In seven studies, all the included patients had NSCLC.[24,25,27,29,30,36,37] In the remaining six, patients with NSCLC comprised a subgroup (34%–86%).[26,28,31–35]

Bisphosphonates Evaluated. All the studies except two evaluated the effect of zoledronic acid.[24–29,31,32,34–37] The remaining two studies evaluated clodronate and ibandronate, respectively.[30,33] In all the studies patients also received systemic anticancer treatment.

Study Designs Used. Only two phase III studies including a subgroup of patients with NSCLC (44.0%–48.9%) were found; pain was evaluated as a secondary end point or in an ad hoc analysis, and QoL was not evaluated. Subgroup analyses for patients with NSCLC were not performed; SREs were the primary end point.[28,34,35] Two studies had a retrospective design.[25,32] Nine studies were either phase II studies or their design was not clear. Four of the nine studies were two-arm studies,[27,29,33,37] although only one of them was a randomized double-blind study.[33] One randomized study did not clearly specify whether it was a blinded study.[27] In another study the groups were unbalanced: one arm consisted of patients with bone pain (they were treated with zoledronic acid), and the other arm consisted of patients without bone pain (they did not receive zoledronic acid).[37] In the final study patients who had not consented to participate in it were used as the control group.[29]

Methods of Pain Measurement. Measurements of pain varied between studies and consisted, for example, of the visual analogue scale (VAS),[25,33,37] the Brief Pain Inventory (BPI),[26,28,32,34–36] analgesic consumption diaries,[24,26,28,30,31,33–35] or a six-point pain intensity scale.[27] Frequency of pain evaluation varied between every 3 and every 6 weeks. Pain was evaluated in all the studies, although in one study it was evaluated only as a part of the Lung Cancer Symptom Scale (LCSS).[29]

Methods of QoL Measurement

QoL was evaluated in only five studies. The evaluation methods used were the Functional Assessment of Cancer Therapy–G,[26,34,35] the European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire C30,[25,32] and the LCSS.[29] In one study the short version of the BPI was used to measure extent to which pain interfered with daily life, which served as a surrogate for QoL.[28]

Radioisotopes

Twelve radioisotope studies were found. All were prospective, although the phase of the study was not always clearly documented.[22,38–48]

Included Patients. None of the studies included only patients with NSCLC, although in two studies the other patients included all had SCLC.[43,48] In five other studies the exact number of patients with NSCLC in the lung cancer subgroup was not clear.[38,41,44,46,47]

Radioisotopes Evaluated and Study Design Used. In five studies samarium was evaluated (two phase I or II studies, one phase III study, and two single-arm studies with the phase unknown); single doses varied between 3.7 MBq/kg and 111 MBq/kg and treatments were repeated when necessary.[38,40,44,46,47] Only one single-arm study for strontium was found; it involved a single dose of 150 MBq/kg (repeated when necessary).[41] In the remaining six studies rhenium (^{186}Re or ^{188}Re) was evaluated. All the studies except one were single-arm phase II studies, and the mean single doses varied between 1158 MBq/kg and 1295 MBq/kg. Again, treatment could be repeated when necessary.[22,42,43,45,48] In the other study (phase I) escalating doses from 20 to 50 MBq/kg were used.[39]

Methods of Pain Measurement. For pain measurement, the VAS,[38–40,43] a composite pain score,[41,44] a score combining the effect on pain intensity and time until a decrease in pain,[47] and a three- or four-point pain scale were used,[45,48] as were analgesic consumption scores.[39–41,43] When mentioned, the frequency of evaluations was mostly weekly for the first months with a lower frequency (once or twice a month) thereafter.[22,39,43,45,47,48] Responses were not always clearly defined, but in general, they consisted of a decrease in pain score or analgesic consumption score.

Methods of QoL Measurement. Only one study included a surrogate outcome measure (sleep duration, mobility, mood, and daily activities) for QoL.[43]

Results

Bisphosphonates and Denosumab: Effect on Pain

The results are summarized in Table 4. Time of onset of pain reduction was provided in only two studies: after six cycles (each cycle lasted 3 to 4 weeks) and after 1 month, respectively.[26,27] In the two randomized studies of zoledronic acid (one versus placebo, one versus ibandronate), there were no significant differences in pain score between the groups.[27,34,35] In one of these studies, however, the BPI score for the subgroup of patients with pain at baseline decreased at 9 months (significance unknown), although no subgroup analysis of the pain of patients with NSCLC was performed.[34,35] In the other study (limited to patients with NSCLC), there was a trend toward a faster decrease in pain in the zoledronic acid group after 1 month ($p = 0.05$) than in the ibandronate group, although there was no significant difference in pain at 3 months ($p = 0.31$). Of the patients in the two studies, 61% and 56%, respectively, had a decrease in pain score of two or more points at 3 months (on a six-point pain intensity scale).[27] In the one study in which patients with NSCLC who refused to enter the study served as a control group, the patients treated with zoledronic acid manifested less need for radiation and a trend toward less pain ($p = 0.08$) compared with those in the control group.[29] No difference in pain effect was found in an imbalanced study that included patients with NSCLC with bone pain in one group and patients with NSCLC without bone pain in another group.[37] In all the single-arm studies of zoledronic acid, a decrease in pain score, analgesic use, or both was found for some of the patients (decrease in pain score 38%–77%, decreased or stable analgesic use 58%–75%), especially in the case of those patients with moderate or severe pain at baseline. Patients were also treated with chemotherapy. In the three studies not limited to patients with NSCLC, no subgroup analysis was performed for NSCLC.[26,31,32] In the randomized study examining clodronate versus placebo, a significantly lower increase in analgesic use was found (18% versus 54%) for the clodronate group, although the pain scores were not significantly different.[33] In the single-arm study of ibandronate (plus chemotherapy), 16% of patients had a reduced need for analgesics and 59% a stable need. Pain scores were not provided.[30] In the randomized study of denosumab versus zoledronic acid, the patients who were treated with denosumab and had no pain or mild pain at baseline exhibited a significantly longer time before experiencing more than a four-point increase in BPI score than did the patients treated with zoledronic acid ($p = 0.05$), and their analgesic use was lower. Also, patients without severe pain at baseline took a significantly longer time to reach a two-point or greater increase in BPI score ($p = 0.016$). Subgroup analysis for NSCLC was not performed.[28]

Because of the different methods and time points used for pain evaluation, it was not possible to perform a meta-analysis. Of the 2606 patients included in the studies, 1217 were diagnosed with NSCLC. When the results are summarized for the studies that included only patients with NSCLC or in which a subgroup analysis was performed for patients with NSCLC, a total of 489 patients with NSCLC were evaluated (seven studies, four with one arm and three with two arms [one unbalanced]).[24,25,27,29,30,36,37] The results are summarized for the patients for whom data were available. Of those patients, 26% (range 16%–36%) had a decrease in pain medication used, 25% had an increase in analgesic consumption, and the others had a stable need for such medications (two studies, N = 85).[24,30] A mean of 66.7% of patients (range 60%–77%) reported a decrease in pain score (three studies with a total of 225 patients); however, only in one study (N = 35) was this decrease further specified: the mean BPI score decreased 2.6 points from baseline to a mean score of 1.0 after 6 weeks.[25,27,36] In one other study (N = 35), the LCSS pain score remained stable in the zoledronic acid group but decreased by 20 points in the no–zoledronic acid group (a higher score indicates less pain).[29] In this study, patients treated with zoledronic acid received less radiotherapy than did patients not treated with zoledronic acid (16.7% versus 70.6%).[29]

Bisphosphonates and Denosumab: Effect on QoL

In two of the five studies evaluating QoL, a significant improvement in QoL was found. They were single-arm studies, and in the study not limited to patients with NSCLC, subgroup analysis was not performed.[25,26] In the study of denosumab versus zoledronic acid, the time until an increase in the extent to which pain interfered with daily life (used as surrogate for QoL) was longer in patients treated with denosumab and with no pain or mild pain interference at baseline. Subgroup analysis for NSCLC was not performed.[28]

Radioisotopes: Effect on Pain

The results are summarized in Table 5. In the case of samarium, 60% to 95% of patients experienced a decrease in pain. When mentioned, onset of pain reduction occurred within approximately 1 week.[38,40,44,46,47] However, only two of five studies reported on NSCLC separately.[40,47] In one study, only 20% of patients with NSCLC responded (40% had no response and the remaining 40% were not evaluable owing mainly to early death).[40] In the other study, however, no differences in pain relief between subgroups were found, and the

Table 4. Outcomes of the Trials Examining Bisphosphonates and Denosumab

Trial, y	R or P	Total Patients/ Patients with NSCLC	Arms Specified when Necessary	Pain/QoL Outcome for Total Group or NSCLC Subgroup Also?	Outcome: Pain	Outcome: QoL
Bisphosphonates						
Piga, 1998	P	66/17	A: clodronate B: placebo	No	*Overall* - Response rate not mentioned, no significant differences in pain score (although 1.1-point decrease in arm A and 1.3-point increase in arm B, $p = 0.42$) - Onset/duration of pain reduction not mentioned - Analgesics: increase in 18.5% of patients in arm A vs. in 54.4% in arm B, $p = 0.04$	Not provided
Rosen, 2003, update follow-up: Rosen, 2004	P	773/378	A: CT with ZOL B: CT with placebo	No	*Overall* - Response rate not mentioned, slight increase in mean BPI score from baseline to 9 mo for all groups, mean composite score decreased for arm A patients with pain at baseline - Onset/duration of pain reduction not mentioned - Analgesics: for both groups increase in analgesic use	For both groups decrease in functional capacity
Kiaga, 2006	P	32/32	CT with IBA	Total group (patients with NSCLC only)	*Overall (patients with NSCLC)* - Response rate not mentioned - Onset/duration of pain reduction not mentioned - Analgesics: 16% of patients had reduced need for analgesics, 59% had stable need, and 25% had increased need	Not provided
Facchini, 2007	P	60/28	CT with ZOL	Total group (16 patients excluded for not completing study)	*Overall* - Response: 77.2% of patients had moderate or greater pain at baseline vs. 29.5% after 12 cycles (48 wk) ($p < 0.001$) - Onset of pain reduction: after 6 cycles - Duration of pain reduction: at least until wk 48 (end of study) - Analgesics: maximum decrease after 3 cycles ($p = 0.006$), then steady state	Significant improvement in QoL ($p = 0.02$)
Kotteas, 2008	P	86/74	CT with ZOL	Total group	*Overall* - Response rate, see analgesics - Onset/duration of pain reduction not mentioned - Analgesics: after 3 cycles (86 patients): 8.1% of patients had reduced need, 57% had stable need, and 34.8% had increased need; after 6 cycles (52 patients): 5.8%, 59.6%, and 34.6%, respectively	Not provided
Longo, abstract only, 2008	R?	24/18 (others SCLC)	CT with ZOL	Total group	*Overall (patients with lung cancer)* - Response rate not mentioned; severe pain at baseline: "remarkable decrease"; low-grade pain at baseline: "greater flare-up after first dose of ZOL" - No mention of onset/duration of pain or analgesics	"Remarkable worsening of several functions and a stability of the emotional one."

(continued)

Table 4. Continued

Trial, y	R or P	Total Patients/ Patients with NSCLC	Arms Specified when Necessary	Pain/QoL Outcome for Total Group or NSCLC Subgroup Also?	Outcome: Pain	Outcome: QoL
Zarogoulidis, 2009	P	144/144	A: bone pain, CT with ZOL B: bone pain, CT only	Total group (patients with NSCLC only)	*Overall (patients with NSCLC)* - Response: "no statistically significant difference between the 2 patient groups regarding to the pain effect of ZOL compared with at baseline ($p > 0.05$)" (time point for comparison of both groups not mentioned) - Onset/duration of pain reduction not provided - Analgesics not provided	Not provided
Francini, 2010	P	55/55	A: CT with ZOL B: CT with IBA	Total group (patients with NSCLC only)	*Overall (patients with NSCLC)* - Response rate not mentioned - Onset of pain reduction: at 1 mo trend to more rapid decrease in pain in ZOL group ($p = 0.05$) - Duration of pain reduction: maximum pain relief at 3 mo: no difference ($p = 0.31$), patients with $\geq$2-point increase in pain relief at 3 mo: 61% vs. 56% - Analgesics: difference between groups not mentioned	Not provided
Ishiwata, 2011	P	35/35	A: CT with ZOL B: CT	Total group (patients with NSCLC only)	*Overall (patients with NSCLC)* - Response rate not mentioned - Onset of pain relief: at 8 wk pain relief higher in group A ($p = 0.03$), at 16 wk trend to more pain relief in group A ($p = 0.08$) - Duration of pain relief not mentioned - Analgesics not mentioned - Radiation treatment at 3 mo: group A 16.7% of patients, group B 70.6% ($p = 0.001$)	"No significant difference"
Del Signore, 2012 (abstract only)	R	135/135	CT with ZOL	Total group (patients with NSCLC only)	*Overall (patients with NSCLC)* - Response: "bone pain in 80% of patients, in 60% decrease in pain during treatment" - Onset/duration of pain relief not mentioned - Analgesics not mentioned	"improved QoL," not specified
Yoh, 2012	P	35/35	CT with ZOL	Total group (patients with NSCLC only)	*Overall (patients with NSCLC)* - Response 27 patients (77%) improved in BPI, mean score at baseline 2.6, after 6 wk 1.0 ($p < 0.0001$) - Onset/duration of pain relief not mentioned (only measurements at baseline and 6 wk) - Analgesics not mentioned	Not provided
Davidov, 2013	P	53/53	CT with ZOL	Total group (patients with NSCLC only)	*Overall (patients with NSCLC)* - Response rate not mentioned - Onset/duration of pain relief not mentioned - Analgesics: 35.9% of patients had reduced need, 39.6% had stable need, 24.5% had increased need after 6 cycles - Additional radiation therapy: 6 patients (11.3%) for pain	Not provided

(continued)

Table 4. Continued

Trial, y	R or P	Total Patients/ Patients with NSCLC	Arms Specified when Necessary	Pain/QoL Outcome for Total Group or NSCLC Subgroup Also?	Outcome: Pain	Outcome: QoL
Denosumab vs. bisphosphonates						
Henry, 2014	P	1597/702	A: denosumab + placebo B: ZOL + placebo	Only total group	*Overall* - Response rate not mentioned - Onset of pain relief not mentioned - Duration: All patients without severe pain at baseline: median time to ≥2-point increase in BPI-SF pain interference score: arm A 5.6 vs. arm B at 4.6 mo, $p = 0.016$. Median time to ≥2-point decrease in BPI-SF score not different (2.8 mo). No/mild baseline pain: time to > 4-point increase in BPI-SF score 4.7 mo (arm A) vs. 3.7 mo (arm B), $p = 0.050$ - Analgesic use less in arm A for patients with no/mild baseline pain at each time point	Surrogate: pain interference, no/mild baseline pain interference: time to ≥2-point increase in BPI-SF pain interference score 8.2 (arm A) vs. 4.8 (arm B) mo, $p = 0.021$

R, retrospective; P, prospective; NSCLC, non-small cell lung cancer; QoL, quality of life; CT, chemotherapy; ZOL, zoledronic acid; BPI, Brief Pain Inventory; IBA, ibandronate; SCLC, small cell lung cancer; BPI-SF, Brief Pain Inventory-Short Form.

response rates were greater than 80%.[47] When mentioned, mean duration of pain relief was between 1 and 3.8 months.

In the subgroup of patients with lung cancer who were treated with strontium (n = 24), all patients experienced pain relief and a reduction in analgesic use. Onset of pain reduction was not mentioned; the mean duration was 3.3 months.[41]

Between 62% and 84% of patients with NSCLC or lung cancer who were treated with rhenium had a decrease in pain, and approximately 35% had a complete response.[22,39,45,48] One of the studies did not mention the response percentage; the decrease in VAS score was 3.5 points. Time until onset of pain relief was not mentioned for the lung cancer subgroup; for the total group, it was within 1 week.[43] One study that included five patients with lung cancer reported results conflicting with the aforementioned results. In it, improvement in performance score was used as a surrogate for pain. Only two patients (40%) responded, one with a 75% improvement in performance score and one with a 20% improvement.[42] Only one study of rhenium mentioned the duration of the response of patients with NSCLC (median 10 weeks).[22] In the other studies, the duration of the response of the total group ranged from 1 to 3 months.[39,43,45]

In the aforementioned studies, a total of 713 patients were treated with radioisotopes, NSCLC was diagnosed in 199 (in 72 of 199 cases the diagnosis not specified further than "lung cancer"). The 10 studies that were limited to patients with NSCLC or in which a subgroup analysis for patients with NSCLC was performed included a total of 170 patients with NSCLC (all except two were single-arm studies).[22,39-43,45-48] Seven studies (N = 117) mentioned a response percentage: a mean of 65.7% of patients responded (range 20%–100%).[12,22,39-41,45,48] Only two studies (N = 48) mentioned duration of response (mean 2.9 months).[22,41] Two studies (N = 56) reported on analgesic intake; a mean of 79.9% of patients had a decrease (range 59.7%–100%).[41,48] Pain scores were reported in two studies (N = 12); the mean decrease was 2.2 points (3.75 points when only the highest dose of samarium was taken into account).[43,46]

Radioisotopes: Effect on QoL

In the only study in which QoL was specified in the Methods section (daily functioning served as a surrogate), 91% of patients improved. A subgroup analysis for NSCLC was not performed.[43] Although one study did not include a description of the method for evaluation of QoL, its authors stated in their results that "responding patients had an improvement in QoL."[47] The other studies did not report on QoL.

Discussion

In this systematic review, no randomized studies evaluating bisphosphonates or denosumab in NSCLC with pain, QoL, or both as a primary end point were found; moreover, most studies did not include measurements of QoL. Therefore, no high-level evidence that one of these agents reduces or prevents pain or improves QoL was found. In one randomized study (zoledronic acid versus ibandronate) that included only patients with NSCLC, there was a trend toward a more rapid decrease in pain in the zoledronic acid group; however, at 3 months this difference had disappeared.[27] In the other randomized studies, no NSCLC subgroup analyses with respect to pain and QoL were performed.[28,33-35] In the single-arm studies of zoledronic acid, a decrease in pain and analgesic consumption was found for some of the patients (38%–77%).[26,30,31,36] Patients were also treated with chemotherapy, and the effects of the separate treatments are not clear. In the study of denosumab versus zoledronic acid, which did not include a subgroup analysis for NSCLC, it was found that in particular, patients with no pain or mild baseline pain have a longer time until an increase in pain when treated with denosumab than when treated with zoledronic acid.[28]

Most studies did not include QoL measurements, and an improvement in Qol was found in only two of the five studies that did.[25,26]

The effect of bone-targeted agents seems to be tumor dependent; however, no phase III trials that included patients with NSCLC only, regardless of the primary end point, were found.

In most studies, the primary end point was prevention or delay of onset of SREs. Although pain and QoL are important issues for patients, they are not included in the definition of SRE. Furthermore, pain treatment can be subdivided into semidirect pain relief after administration of a drug (e.g., a treatment effect within 1 week) and long-term prevention of pain or prevention of an increase in pain. Direct effects in the form of pain reduction were not mentioned; pain reduction or prevention was not uniformly reported (the time points evaluated varied from 1 to 9 months). Palliative radiotherapy can be used as an indirect measure of bone pain, but the decision regarding when to use radiotherapy is a subjective one and also dependent on local policies. Moreover, radiotherapy can be used only for one or a few painful bone metastases. Furthermore, palliative radiotherapy has minimal toxicity; only a limited number of visits to the clinic are needed, and radiotherapy is often highly effective in controlling bone pain.[49]

It seems that radioisotopes (samarium, strontium, and rhenium) have a palliative effect on pain with a rapid onset of action and duration of response of approximately 1 to 3 months. However, the data on NSCLC are limited and consist of subgroup analysis of mostly phase I and II studies. There was only one randomized, placebo-controlled phase III trial, and lung cancer was diagnosed in only six of its 118 patients. The other radioisotope studies did not include a placebo arm, and it is likely that at least part of the observed pain relief was due to the placebo effect. Because radioisotope treatment can be repeated, the relatively short duration of response does not seem to be problematic. However, radioisotopes can cause bone marrow suppression, and combining them with palliative systemic therapy is not advisable. Therefore, radioisotopes seem to be an option only when patients do not receive active anticancer therapy and have bone pain that is not eligible for palliative radiotherapy.

Most of the current NSCLC guidelines include some recommendations regarding bone-targeted agents and bone metastases. Zoledronic acid is the only bisphosphate with regulatory approval for the prevention of SREs. The National Comprehensive Cancer Network guideline (2015), National Institute for Health and Care Excellence lung cancer guideline (2011), and European Society for Medical Oncology guideline for NSCLC (2014) all recommend that zoledronic acid or denosumab be used in patients with bone metastases. When mentioned, such use is to prevent SREs.[4,6,7] In the European Society for Medical Oncology clinical practice guideline on bone health in patients with cancer (2014), this advice is further refined. Zoledronic acid or denosumab are advised in selected patients with lung cancer who are at high risk for occurrence of SREs and have a life expectancy of more than 3 months.[5] Pain reduction or prevention of an increase in pain is not mentioned. Neither do the aforementioned guidelines discuss the potential use of radioisotopes.

In daily practice, bone-targeted agents are prescribed to reduce time until occurrence of a SRE, reduce number of SREs, and indirectly reduce or prevent pain and a decrease in QoL. Pain relief from bisphosphonates is suggested in a fairly recent (2009) expert panel consensus.[50] The panel refers to the randomized study of Rosen et al.,[35] which does not specify pain relief for the NSCLC subgroup, however.

As is clear from our systematic review, there is no high-level evidence that zoledronic acid or denosumab have an effect on pain or QoL in patients with NSCLC. Even when present, onset of pain relief is unclear. In the recent literature, moreover, whether use of SREs is the most clinically relevant end point for patients is also questioned. It is suggested that a more holistic approach and more patient-centered outcomes—symptomatic skeletal events (SSEs)—be used instead of SREs (SSEs are SREs, but without asymptomatic pathological fractures).[10] So, to decide whether bone-targeted agents are useful, one should take into account not just patient-centered

Table 5. Outcomes of Tials Examining Radioisotopes

Trial, y	R or P	All Patients/ Patients with NSCLC	Arms Specified when Necessary	Pain/QoL Outcome for Total Group or Also NSCLC Subgroup?	Outcome: Pain	Outcome: QoL
Farhanghi, 1992	P	22/5	Sm-153-EDTMP	Also NSCLC subgroup (only for response)	*Overall* - Response rate: 65.4% - Onset of pain reduction: not mentioned - Duration: mean 3.8 mo - Analgesics: 18.2% discontinued analgesics *NSCLC* - Response rate: 20% (40% no response, 40% not evaluable)	Not provided
Alberts, 1997	P	28/9 ("lung cancer")	Sm-153-EDTMP	No	*Overall* - Response rate: 78%-95% of patients had improvement in pain - VAS: median 4-point decrease - Onset of pain reduction: usually at $\leq$48 h - Duration: median 31-56 d	Not provided
Kasalicky, 1998	P	118/31 ("lung cancer")	^{89}SRCl	Also "lung cancer" subgroup	*Overall* - Response rate: 96.6%, (near) complete 78.8% - Duration: mean 3.3 mo - Onset of pain reduction: not mentioned - Analgesics: decreased in 94.1% of patients, 2.6% discontinued analgesics *Lung cancer* - Response rate: 100%, (near) complete 90% - Duration: mean 3.3 mo - Onset of pain reduction: not mentioned - Analgesics: 100% of patients had a decrease in use	*Overall* Improvement in general condition 96.6% *Lung cancer* Improvement in general condition 100%
Serafini, 1998	P	118/6	A: Sm-153-EDTMP, 18.5 MBq/kg B: Sm-153-EDTMP, 37 MBq/kg C: placebo	Also NSCLC subgroup (only for AUPC-VAS)	*Overall* - Response at wk 4: A, 65%; B, 62%; C, 40% - Duration: not specifically mentioned, lasting until wk 16 for most patients in Group B, almost none in Group C - Onset of pain reduction: within 1 wk - Analgesics use at wk 4: $\pm$35% decrease in group A, $\pm$20% decrease in group B, $\pm$20% increase in group C *Lung cancer* - In arm A, +1 on AUPC-VAS at 4 wk; in arm B and C, respectively, -4 and + 4	Not provided

(continued)

Table 5. Continued

Trial, y	R or P	All Patients/ Patients with NSCLC	Arms Specified when Necessary	Pain/QoL Outcome for Total Group or Also NSCLC Subgroup?	Outcome: Pain	Outcome: QoL
Tian, 1999	P	105/41 ("lung cancer")	A: Sm-153-EDTMP, 37 MBq/kg B: Sm-153-EDTMP, 18.5 MBq/kg	Mentioned only that subgroup analysis per primary tumor was performed	*Overall:* - Response rate: arm A 82.9%, arm B 85.7% - Duration: mean 8.6 wk in both arms - Onset of pain reduction: mean 8.78 d - SEP: group A 22.3, group B 20.1 - Analgesics: dose reduction/cessation in 55.7% of patients in arm A and 68.6% in arm B *NSCLC* - "No differences for subgroup analysis" - SEP: 17 for both arms	Not provided in detail: "QoL increased in responding patients"
Küçük, 2000	P	31/5	Re-186-HEDP	Also NSCLC subgroup	*Overall:* - Response rate: 67.5% - Duration: mean 8.1 wk - Onset of pain reduction: not mentioned *NSCLC* - Response rate: 20% (1 patient) major response, 20% (1 patient) minor response - Duration and onset: not provided	Not provided
Li, 2001	P	61/26	Re-188 HEDP	Also NSCLC subgroup (only for response)	*Overall:* - Response: 36% complete response, 44% significant response - Duration: 1–3 mo - Onset of pain reduction within 1 wk for 80% - Number of treatments for pain: 1 (62%), 2 (16%), others 3–6 *NSCLC:* - Response rate: 77% - Duration/onset of pain relief: not mentioned	Not provided
Li, 2002	P	66/20 ("lung cancer")	Sm-153-EDTMP	No	*Overall* - Composite score: CR 25.7%, PR 36.4%, NE 37.9% - Duration/onset of pain relief: not mentioned	Not provided
Zhang, 2003	P	30/25 (others SCLC)	Re-188-HEDP	Also NSCLC subgroup (only for pain relief, not for analgesic intake)	*Overall:* - Response rate: 80% of patients had pain relief, 33% had complete response *NSCLC:* - Response rate: 84% pain relief, 36% complete response - Onset of pain reduction: within 1 wk - Analgesics: analgesic intake discontinued by 46.7% of patients, decreased by 13%, remained stable by 16.7%, and increased by 23.3%	Not provided

(continued)

Table 5. Continued

Trial, y	R or P	All Patients/ Patients with NSCLC	Arms Specified when Necessary	Pain/QoL Outcome for Total Group or Also NSCLC Subgroup?	Outcome: Pain	Outcome: QoL
Leondi, 2004	P	24/6 (others SCLC)	Re-186-HEDP	Also NSCLC subgroup (only for VAS)	*Overall:* - Response rate: 95.8% pain relief, 37.5% complete - VAS: Mean difference before and after treatment: -3.7. clinically significant (-3 VAS) - Duration mean 1.5 mo - Onset of pain relief: within 1 wk in 62%, - Analgesics: 77% of patients reduced opioid intake *NSCLC:* - VAS: mean difference before and after treatment -3.5 - Duration and onset of pain relief: not mentioned	91% of patients had improvement in sleep, mobility, mood, communication ability
Minutoli, 2006	P	41/17	Re-186-HEDP	Also NSCLC subgroup	*Overall* - Response rate: 85.4% (49% complete) - Duration: median 10 wk - Onset of pain reduction: within 1 or 2 wk *NSCLC* - Response rate: 76.5% (35% complete) - Duration: median 10 wk - Onset of pain relief: not mentioned	Not provided
Cheng, 2011	P	64/8	Re-188-HEDP	Also NSCLC subgroup (only for pain relief)	*Overall* - Response rate: 73.3% (10% complete) - VAS: after 4 wk -3.22 from nadir, after 8 wk +1.78 from nadir - Duration of pain relief: mean 6.9 wk - Onset of pain reduction: within 1 wk *NSCLC* - Response rate: 62.5% - Onset/duration of pain relief: not mentioned	Not provided

R, retrospective; P, prospective; NSCLC, non-small cell lung cancer; QoL, quality of life; EDTMP, ethylenediaminetetra(methylene phosphonate); HEDP, 1-hydroxy ethylidene-1,1-diphosphonic acid; AUPC-VAS, area under the pain curve-visual analogue scale; SEP, sum of effect product; CR, complete response; PR, partial response; NE, not evaluable.

outcomes such as pain and QoL but also survival, response (SRE or SSE), and toxicities.

In conclusion, the evidence that bisphosphonates or denosumab reduce or prevent pain in patients with NSCLC with bone metastases or that they have an influence on QoL is very scant. Radioisotopes seem to have a palliative effect on pain with a rapid onset of action, although there is no high-level evidence of such an effect.

Our opinion is that there is room to evaluate the clinical benefit of bisphosphonates or denosumab in patients with NSCLC with bone metastases. The primary end point should consist of a patient-relevant outcome—for example, a composite end point of frequent measurements of pain and QoL combined with determination of the incidence of clinically relevant fractures and spinal cord compression. Such a study should include patients with NSCLC only, and it should be a randomized, double-blind study to exclude the effects of palliative systemic therapies (chemotherapy as well as targeted therapies) on these outcomes, especially the "weak" end points such as pain and QoL. Pain relief should be measured by standardized, reliable questionnaires (e.g., the Bone Metastases Quality-of-Life Questionnaire and the Bone-Metastases-22 module of the European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire C30).[51,52]

Appendix. The Search Strategy

PICO Components		Search Terms	
Patient		*NSCLC*	OR
		Non-small cell lung cancer	
		AND	
		Bone metastases	OR
		Bone neoplasm	
Intervention	AND	*Bisphosphonates*	OR
		Zoledronic acid	
		Radionuclide	
		Strontium	
		Samarium	
		Rhenium	
		Radioisotopes	
		Radioactive-labeled bisphosphonates	
		Bone-targeted agents	
		Denosumab	
		Rank ligand	
Comparator		Not specified in search strategy to allow inclusion of single-arm studies	
Outcome		Not specified in search strategy to allow inclusion of studies in which pain was not a primary outcome	

PICO, patient, intervention, comparator, outcomes; NSCLC, non-small cell lung cancer.

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