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Denosumab in patients with cancer and skeletal metastases: A systematic review and meta-analysis

Prashanth Peddi [a], Maria A. Lopez-Olivo [a], Gregory F. Pratt [b], Maria E. Suarez-Almazor [a,*]

[a] Division of General Internal Medicine, The University of Texas, MD Anderson Cancer Center, Houston, TX, USA
[b] Research Medical Library, The University of Texas, MD Anderson Cancer Center, Houston, TX, USA

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ABSTRACT

Background: We conducted a systematic review of the literature to determine the efficacy and safety of denosumab in reducing skeletal-related events (SRE) in patients with bone metastases.
Methods: A literature search using MEDLINE, EMBASE, Web of Science and The Cochrane Collaboration Library identified relevant controlled clinical trials up-to-March 14, 2012. Two independent reviewers assessed studies for inclusion, according to predetermined criteria, and extracted relevant data. The primary outcomes of interest were SRE, time to first on-study SRE, and overall survival. Secondary outcomes included pain, quality of life, bone turnover markers (BTM), and adverse events.
Results: Six controlled trials including 6142 patients were analyzed. Compared to zoledronic acid, denosumab had lower *incidence of SRE* with a risk ratio (RR) of 0.84 (95% confidence intervals (CI) 0.80–0.88), delayed *the onset of first on-study SRE* (RR 0.83; 95% CI 0.75–0.90) and *time to worsening of pain* (RR 0.84; 95% CI 0.77–0.91). No difference was observed in *overall survival* with pooled hazard ratio of 0.98 (95% CI 0.90–1.0). For total adverse events, denosumab was similar to zoledronic acid (RR 0.97; 95% CI 0.89–1.0). No significant differences were observed in the frequency of *osteonecrosis of the jaw* (RR 1.4; 95% CI 0.92–2.1). Patients on denosumab had a greater risk of developing *hypocalcemia* (RR 1.9; 95% CI 1.6–2.3).
Conclusions: Denosumab was more effective than zoledronic acid in reducing the incidence of SRE, and delayed the time to SRE. No differences were found between denosumab and zoledronic acid in reducing overall mortality, or in the frequency of overall adverse events.

Introduction

Metastatic involvement of bone is a common complication of advanced cancer. Nearly 100% of patients with myeloma, 65–75% of patients with breast or prostate cancer, and 30–40% of those with lung cancer develop skeletal metastases.[1] Half of these patients develop one or more complications collectively termed skeletal-related events (SRE) (i.e. bone pain, hypercalcemia, fracture, spinal cord compression, radiotherapy requirement for pain, and surgery for pathological fracture).[2,3] Since 2002, incidence of SRE has been used as the composite primary endpoint in the trials conducted to reduce skeletal complications among patients with bony metastases.[4,5] SRE cause significant morbidity reduced performance status, quality of life (QOL) and reduced survival.[6,7] They are estimated to cost 1.9 billion dollars every year in the United States, with the cost to treat a single SRE episode per patient varying from 6973 to 11,979 USD.[8–10]

In addition to treating the primary cancer, bisphosphonates therapy has become an important strategy to reduce SRE among patients with myeloma, and bone metastases from breast, prostate and lung cancer.[11–14] However, bisphosphonates reduce SRE by only 30–40% in patients with skeletal metastases, cause infusion-related reactions, osteonecrosis of the jaw (ONJ), and require intravenous administration and frequent renal monitoring.[15–17]

Receptor-activated nuclear factor kappa-B ligand (RANKL), one of the mediators of osteoclast differentiation, also attracts tumor cells into the bone, which in-turn interact with marrow stromal cells to produce more RANKL, creating a vicious cycle of osteoclast activation and bone destruction.[18–21] Denosumab, a monoclonal antibody against RANKL, has shown efficacy in reducing osteolytic markers and SRE. It is administered as a subcutaneous injection and is not excreted through the kidney, a potential advantage compared to bisphosphonates for patients with chronic kidney disease.

Patients with metastatic breast, prostate and other cancers are living longer with the advent of newer and targeted therapies. Therefore, the role of supportive therapy to prevent and treat these bone complications is becoming more relevant. We conducted a systematic review and meta-analysis to evaluate the efficacy and safety of denosumab among patients with metastatic bone disease.

* Corresponding author. Address: The University of Texas, MD Anderson Cancer Center, T. Boone Pickens Academic Tower (FCT13.5034), 1515 Holcombe Blvd., Unit 1465, Houston, TX 77030, USA. Tel.: +1 713 745 4516; fax: +1 713 563 4491.
E-mail address: msalmazor@mdanderson.org (M.E. Suarez-Almazor).

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Methods

Data sources and search strategy

We searched MEDLINE, EMBASE, the Cochrane Collaboration Library, and Web of Science with no language restrictions up to March 14, 2012. References of the included articles were also searched manually. The search strategy is provided in Appendix A.

Study selection

Titles and abstracts of all retrieved citations were screened by two independent reviewers (GP and PP) to identify potentially relevant studies. Full texts were retrieved for relevant citations. Disagreements were resolved by consensus.

Inclusion criteria

Controlled clinical trials evaluating the efficacy of denosumab (at any dosage or frequency) for the treatment of cancer patients with skeletal metastases or myeloma were included, if they met the following criteria. (1) Participants of 18 years or older; and (2) Report of at least one of the following outcomes: (a) Incidence of SRE, (b) Time to first on-study SRE, (c) Overall survival, (d) Overall disease progression, (e) Percent reduction in bone turnover markers (BTM), or (f) Adverse events (AE).

We did not exclude studies based on trial duration or length of follow-up. Case reports, editorials, letters to the editors and studies with no comparison group were excluded. Abstracts of the conference proceedings were included if the journal article for the corresponding studies have not been published.

Data extraction

Primary outcomes were: (1) SRE, defined as pathological fracture (excluding major trauma), radiation therapy to bone, bone surgery or spinal cord compression. Hypercalcemia and pain were not included in this definition. We evaluated both incidence of SRE and time to first on-study SRE; (2) Overall survival (OS), defined as the time period from the point of entry into the study until death; and (3) Overall disease progression was analyzed, as reported by authors. Secondary outcomes included: (1) Pain evaluated as time to worsening, time to improvement, and time to improvement in physical activity, outcomes of pain were measured by any validated pain instrument or using visual analog scale [22,23]; (2) Health-related quality of life (HRQL) was defined as the meaningful improvement in the composite scores of any instrument (MDASI or SDS) assessing physical, social, mental and functional wellbeing of an individual [24,25]; (3) BTM such as urine N-telopeptide (uNTX) and serum bone-specific alkaline phosphatase (BSAP) are indicators for osteolysis and have shown linear correlation with SRE and death.[22] Percentage reductions in the levels of BTM, proportion of patients who achieved reduction of uNTX >65% and time to achieve reduction in uNTX level >65% or <50 mmol/μmol creatinine were used as indicators to measure bone turnover outcome. uNTX level levels below 50 mmol/μmol creatinine are considered normal in young healthy individuals.[26,27] For patients with bone metastases, these levels are considered to represent a lower risk of developing SRE. The cut off level >65% was chosen based on the median percent reduction published on previous studies (59–65%) [28,29]; and (4) AEs were defined as any unfavorable and unintended sign, symptom, abnormal laboratory finding, or disease associated with therapy. Grade 3 Common Terminology Criteria Adverse Events (CTCAE) requiring treatment discontinuation and serious AE (life threatening or requiring hospitalization) were considered when the information was available: (a) Renal toxicity defined as an increase in blood urea or creatinine, acute or chronic renal failure, or decreased creatinine clearance, or proteinuria; (b) Acute phase reactions defined as flu-like illness or any adverse events occurring within the first 3 days after the infusion; (c) Hypocalcemia was defined as symptomatic or asymptomatic serum calcium below 8 mg/dl; (d) ONJ is defined as appearance of necrotic bone in the oral cavity; and (e) Incidence of new cancers and infections for both groups were analyzed as reported by authors.

Quality assessment

Each article that met eligibility criteria was independently assessed by two reviewers (PP and GP) for quality using the risk of bias tool. Attrition, confounding measurement, performance, selection and conflict of interest were graded as low risk, high risk and unable to determine.[30]

Data synthesis and analysis

All outcomes were pooled using STATA Software (version 11.2, StataCorp, College Station, TX).[31] Dichotomous outcomes included rates or proportions from which pooled relative risk (RR) and 95% confidence intervals (CI) were estimated. Means and standard deviations (SD) were used to estimate mean differences and 95% CI. Medians were used instead of means when means were not reported. Standard deviation was estimated from the inter-quartile range when not available. If SD could not be derived through any method, missing data was imputed from other included studies. Pre calculated effect estimates (i.e. hazard ratio (HR)) and CI were pooled if median and SD were missing for time to event variables.[24] Primary analyses were performed using a fixed effects model (Mantel–Haenszel method), and if there was study heterogeneity ($I^2 > 40\%$), a random effects model was used. Number needed to treat (NNT) was also estimated.

Results

Our initial search identified 1551 unique publications (Fig. 1). Of these, only 14 met the inclusion criteria, providing data on 6 trials. Selection agreement between the two reviewers was 97.5% ($\kappa = 0.7$; Standard Error (SE) 0.02).

Study characteristics

Six trials met our inclusion criteria; three were phase II[28,32,33] and three phase III.[34–36] The efficacy and safety of denosumab was compared with either intravenous zoledronic acid or pamidronate or ibandronate in these trials. The dosages and the frequency of the drugs administered, study population, length of follow-up and reported outcomes are shown in (Table 1).

Risk of bias

All studies were randomized controlled trials and had a low risk for bias for the various items assessed. However, three did not adequately report allocation concealment[28,33,34] and two had open label study design for the drug administered.[28,33] All were funded by industry (Table 2).

Participants

The six trials included 6142 participants, of whom 3191 received denosumab and 2951 received intravenous bisphosphonates (either zoledronic acid or pamidronate or ibandronate).