European Journal of Cancer (2013) 49, 416–430

Available at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.ejcancer.info

Review

Denosumab for treatment of bone metastases secondary to solid tumours: Systematic review and network meta-analysis

John A. Ford [a,*], Rob Jones [b], Andrew Elders [a], Clive Mulatero [c], Pamela Royle [d], Pawana Sharma [a], Fiona Stewart [a], Radha Todd [e], Graham Mowatt [a]

[a] *Health Services Research Unit, University of Aberdeen, Aberdeen, United Kingdom*
[b] *Beatson West of Scotland Cancer Centre, Glasgow, United Kingdom*
[c] *Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom*
[d] *Population Health, University of Aberdeen, Aberdeen, United Kingdom*
[e] *Aberdeen Royal Infirmary, NHS Grampian, Aberdeen, United Kingdom*

Available online 18 August 2012

KEYWORDS
Denosumab
Zoledronic acid
Pamidronate
Neoplasm metastasis
Indirect estimation techniques

Abstract ***Aim:*** To evaluate the evidence for denosumab for the treatment of bone metastases secondary to solid tumours and, using a network meta-analysis, indirectly compare denosumab with bisphosphonates and best supportive care.

Data sources: MEDLINE (1948 to April 2011), EMBASE (1980 to March 2011), Cochrane Library (all sections) (issue 1, 2011) and Web of Science with Conference Proceedings (1970 to May 2011) and additional meeting abstracts (2010 and 2011) were searched.

Study eligibility, participants and interventions: Only randomised controlled trials assessing denosumab, bisphosphonates or best supportive care in patients with bone metastases from any solid tumour were included.

Synthesis: Direct evidence comparing denosumab and zoledronic acid was assessed for breast cancer, prostate cancer and other solid tumours. Denosumab was compared with pamidronate and best supportive care through a network meta-analysis for each tumour type. The primary outcomes were time to first skeletal related event (SRE) and time to first and subsequent SRE. Secondary outcomes were skeletal morbidity rate, pain, quality of life (QoL) and overall survival.

Results: Denosumab was found to be more effective in delaying the time to first SRE and reducing the risk of first and subsequent SRE compared to zoledronic acid, placebo and pamidronate. In breast and prostate cancer, denosumab was effective in reducing skeletal morbidity rate compared with placebo. The lack of published data on pain and QoL meant that firm conclusions could not be made. Denosumab did not appear to have an affect on overall survival.

* *Corresponding author:* Address: Norwich Medical School, Faculty of Medicine and Health Sciences, University of East Anglia, Chancellors Drive, Norwich NR4 7TJ, United Kingdom. Tel.: +44 01224 438089; fax: +44 01224 438165.
E-mail address: john.ford@uea.ac.uk (J.A. Ford).

0959-8049/$ - see front matter
http://dx.doi.org/10.1016/j.ejca.2012.07.016

Limitations: Network meta-analyses are subject to uncertainties and potential biases.
Conclusions: Denosumab is effective in preventing SRE, but the effect on pain and QoL is unclear.

1. Introduction

The impact of bone metastases on cancer patients can be considerable. Complications, reduced mobility, pain and the effects of treatment reduce quality of life significantly. Complications may include pathological fracture, spinal cord compression and hypercalcaemia of malignancy.

Bone-targeted pharmacological treatments aim at preventing complications, reducing pain and improving quality of life. To date bisphosphonates have been the main pharmacological treatment option for patients with bone metastases. Currently licensed bisphosphonates include; zoledronic acid (any advanced malignancy involving bone), disodium pamidronate (breast cancer or multiple myeloma), sodium clodronate (breast cancer or multiple myeloma) and ibandronic acid (breast cancer). Bisphosphonates are administered either intravenously (zoledronic acid, pamidronate or ibandronic acid) or orally (clodronate or ibandronic acid) and have been associated with renal toxicity.[1] In the United Kingdom (UK), the National Institute of Health and Clinical Excellence (NICE) currently recommends the use of bisphosphonates in all patients with bone metastases secondary to breast cancer,[2] patients with hormone resistant prostate cancer with painful bone metastases despite conventional analgesics[3] or as an option in lung cancer with bone metastases.[4] Patients who are not recommended for bisphosphonates would receive standard best supportive care.

Denosumab (Xgeva, Amgen) is a fully human monoclonal antibody, licensed for the prevention of skeletal related events (SRE) in bone metastases from solid tumours. It is administered by sub-cutaneous injection and does not require renal monitoring.[5]

The term 'skeletal related event' is a composite endpoint that has evolved over the past 20 years for use in clinical trials. Recent trials define SRE as pathological fracture (including asymptomatic vertebral collapse), spinal cord compression or need for radiotherapy or surgery to bone.[6–8] Other definitions have included hypercalcaemia or change in anti-neoplastic therapy.

Three pivotal trials have evaluated denosumab compared to zoledronic acid for the prevention of SRE.[6–8] There are no head-to-head trials of denosumab compared with other bisphosphonates or best supportive care. These comparisons are, nonetheless, important because of the wide variation in practice. Some centres use only zoledronic acid, some use a variety of bisphosphonates, while others do not use bisphosphonates at all (especially in cancer other than breast). Therefore the aim of this review is to evaluate the evidence for denosumab for the treatment of bone metastases in solid tumours and, using a network meta-analysis, indirectly compare denosumab with other bisphosphonates and best supportive care.

2. Materials and methods

The review complies with PRIMSA guidelines.[9] A pre-specified protocol has been published on the NICE website.[10]

2.1. Literature search and eligibility criteria

Studies were identified by systematic searching of the following databases; MEDLINE (1948 to April 2011), EMBASE (1980 to March 2011), Cochrane Library (all sections) (issue 1, 2011) and Web of Science with Conference Proceedings (1970 to May 2011). Additional meeting abstracts (2010 and 2011) were identified through searching American Society of Clinical Oncology, American Urological Association and San Antonio Breast Cancer symposium. Reference lists of all included studies were scanned to identify additional potentially relevant studies. The titles and abstracts of all papers identified by the search strategy were screened and full-text copies of all potentially relevant studies obtained.

The search strategy used for MEDLINE was; step (1) exp Diphosphonates, step (2) RANK Ligand, step (3) (denosumab or bisphosphonate* or ibandron* or clodron* or pamidron* or zoledron*).tw., step (4) (radiation or radiotherapy or radionuclide* or hormone therapy or strontium or samarium).ti., step (5) or/1–4, step (6) exp Neoplasms, step (7) (solid tumor or solid tumour* or cancer or carcinoma or myeloma).tw., step (8) or/6–7, step (9) 5 and 8, step (10) exp Bone Neoplasms, step)11) (((bone or osteolytic or lytic) adj lesion*) or (bone adj2 metast*)).tw., step (12) (skeletal or fracture*).tw., step (13) or/10–12, step (14) 9 and 13, step (15) randomized controlled trial.pt., step (16) 14 and 15 and, step (17) limit 16 to the English language.

This search strategy was adapted as appropriate for the other databases.

Only randomised controlled trials evaluating denosumab, bisphosphonates or best supportive care were included. Best supportive care included trials evaluating radiotherapy, radionuclides, hormone therapy,