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Original Article

Incidence of Skeletal-related Events Over Time from Solid Tumour Bone Metastases Reported in Randomised Trials Using Bone-modifying Agents

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Abstract

Aims: Skeletal-related events (SREs) in patients with bone metastases decrease a patient's quality of life and functional status. Although bone-modifying agents have been found to reduce the time to first on-trial SRE and decrease the total incidence of SREs in randomised clinical trials, standard practice in the management of bone metastases has changed concurrently. The purpose of this study was to investigate if advances in bone-targeted therapies have decreased the incidence of individual types of SREs and to delineate the trend of SREs.

Materials and methods: A literature review was conducted in MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials to identify phase III, randomised bisphosphonate and other bone-targeted therapy trials from 1980 to September 2011. For all studies, a mean year of enrolment ([start of enrolment + end of enrolment]/2) was calculated. The incidences of SREs were tabulated and expressed as percentages of on-trial patients. Generalised linear mixed models were used to search for the trends of SREs over time for all placebo and intervention arms. Regression coefficients were interpreted as the odds ratio, which was calculated using the exponential of the slope. Ninety-five per cent confidence intervals were also calculated.

Results: In total, 20 eligible studies were identified that reported SRE data from phase III trials, of which 11 were suitable for the quantitative analysis. Most of the articles included patients with breast cancer and the remaining involved patients with prostate, renal cell, bladder and lung cancer or other solid tumours. Enrolment periods for all included data ranged from 1990 to 2009. Statistically significant overall downward trends in pathological fractures and the need for surgery were seen over time. Also significant differences between intervention and placebo were seen with all SREs.

Conclusion: The decrease in SREs over time may not only be a result of the development of new generation bone-targeted agents, but also due to better systemic management and awareness of events associated with bone metastases.

Key words: Bisphosphonates; bone metastases; orthopaedic surgery; palliative radiation; pathological fracture; skeletal-related events

Introduction

The most common site of metastatic disease in advanced cancer is bone. About two-thirds of patients with advanced breast cancer or prostate cancer and a third of patients with advanced lung cancer develop bone metastases [1,2], which put patients at high risk of developing skeletal-related events (SREs). 'Skeletal-related complications' as a quantifiable clinical end point were first defined as pathological fractures, irradiation of or surgery on bone, spinal cord compression (SCC) or hypercalcaemia of malignancy; they were first applied to studies assessing pamidronate in women with bone metastases from breast cancer [3]. In the past, hypercalcaemia of malignancy was highly prevalent in breast cancer patients with bone metastases [3], but today, it is a condition that is rarely seen due to a better understanding of the disease and the frequent use of anti-resorptive therapies.

Although the definition of SREs has changed over time, in recent literature, SREs are defined as the need for palliative radiation therapy for bone pain, SCC, pathological fractures or a need for surgery, all of which can greatly reduce the quality of life [4]. Patients with bone metastases who experience an SRE are also more likely to experience subsequent SREs, with a patient's risk of experiencing

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increasing numbers of SREs becoming greater as the metastatic disease progresses [5]. In these trials, after a diagnosis of bone metastases, the median survivals are 25 months with breast cancer, 22 months with prostate cancer and 12 months with lung cancer in bisphosphonate trials [1,6–8]. Therefore, as treatment intent for patients with advanced cancer shifts to the preservation of quality of life, traditional end points such as survival are less relevant and the principal goal of therapy becomes symptom relief [9].

The management of bone metastases is becoming increasingly multidisciplinary in nature and many advances have been made to both localised and systemic therapies [4]. In many cases, the treatment of bone metastases entails the individual use or combination of localised therapy (such as external beam radiotherapy), surgery and systemic interventions, including chemotherapy, hormonal therapy and bisphosphonates, among others. Although bone-targeted therapies have been found to prolong the time to first SRE and reduce the rate of SREs [10], the standard of practice has changed in parallel. SREs also incur substantive costs [11] and curtailing SREs will reduce the burden to healthcare systems in terms of both reduced patient morbidity and lower healthcare costs [12]. The aim of this study was to investigate how developments in bone-targeted therapies and changes in standards of practice have affected the incidence of individual SREs over time and to delineate the trend of SREs.

Materials and Methods

A literature search was conducted in MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials from 1980 to September 2011, on the OvidSP platform, to identify phase III results from bisphosphonate and other bone-targeted therapy trials. The following medical subject headings and text words were used: 'exp neoplasms', 'cancer', 'carcinoma', 'tumor', 'malignan:', 'bone neoplasms/sc' (secondary), 'bone metast:', 'osseous metast:', 'bone pain', combined with 'exp diphosphonates', 'bisphosphonate', 'exp alendronate', 'alendronate', 'alendronic acid', 'exp clodronic acid', 'clodronic acid', 'clodronate', 'dichloromethylene', 'exp etidronic acid', 'etidronic acid', 'etidronate', 'exp ibandronate', 'ibandronate', 'ibandronic acid', 'pamidronate', 'aredia', 'exp zoledronic acid', 'zoledronic acid', 'zolendronate', 'zometa' and 'denosumab' . These terms were then combined with the search terms for the following publication types and study designs: practice guidelines, systematic reviews, meta-analyses, reviews, randomised controlled trials and controlled clinical trials. The literature search was not restricted by language. Studies were limited to phase III trials involving patients with solid tumours, excluding trials in patients with multiple myeloma due to the differences in pathophysiology and therapeutic treatment. Articles reporting the same population data were excluded.

The results of the search were independently sorted for potential inclusion by five co-authors. This process identified 20 eligible studies. The number of SREs that occurred was gathered for all interventions and placebo arms of studies. This included radiation therapy, pathological fractures, SCC, surgical intervention to bone and total SREs experienced. In addition, the intent to treat population of each study was extracted (Table 1) and used to formulate the number of patients who experienced on-trial SREs expressed as a percentage of on-trial patients (Table 2). By

Table 1
Total number of skeletal-related events (SREs) experienced by on-trial patients with specific intervention and study arm sample sizes

Reference	Mean year	Total number of SREs (pamidronate)	Total number of SREs (zoledronic acid)	Total number of SREs (denosumab)	Sample size (any intervention)	Sample Size (Placebo)
[13]	1996	–	–	–	155 with radiotherapy, pathological fracture or spinal cord compression	156 with radiotherapy, pathological fracture or spinal cord compression
[14]	1992.5	79	–	–	185	197
[1]	1993	186	–	–	367	387
[15]	1998.5	42	–	–	182	196
[3]	1992.5	102	–	–	182	189
[16]	2001.5	–	34	–	114	114
[17]	1998.375	–	20	–	28 with radiotherapy, pathological fracture, spinal cord compression or surgery	19 with radiotherapy, pathological fracture, spinal cord compression or surgery
[18] 4 mg	1999.375	–	97	–	257	250
[18] 4/8 mg	1999.375	–	93	–	266	250 (placebo group was used once only)
[8] 4 mg	1999.5	–	71	–	214	208
[8] 8 mg	1999.5	–	85	–	221	208 (placebo group was used once only)
[19]	2011	–	386	341	1901	–
[12]	2006.5	–	372	315	2046	–