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Research Article

Skeletal morbidity rates over time in patients with bone metastases from solid tumors reported in bone modifying agents randomised trials

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ABSTRACT

Objective: Skeletal related events (SREs) are common in patients with bone metastases and lead to decreased quality of life and functional status. The definition of an SRE has evolved over the years and now excludes hypercalcemia of malignancy due to its low incidence. The purpose of this review was to investigate if advances in bone-targeted therapies have decreased skeletal morbidity rates (SMR) over time.

Methods: A literature search was conducted in several databases to identify phase III results from bone-targeted therapy trials from 1980 through September 2011. Graphs were created to document the trends of the natural log of SMR over the mean time of enrolment for all placebo and intervention arms. Statistical hypothesis testing was employed to account for confounding factors.

Results: A total of 14 studies were identified which reported the SMR from phase III trials from 1990 to 2007. A statistically significant downward trend was observed in the placebo arms of trials over time; a similar trend was seen in all intervention arms. In a direct comparison of intervention against placebo arms, it was found that there was a significant decreasing time trend ($p < 0.0001$) and a significant departure in SMR from placebo to intervention arms ($p = 0.0348$). These results were seen even after accounting for the confounding factors of histology and differences in drugs.

Conclusion: The decrease in SMR over time may not only be a result of advancements with bone targeted agents, but also due to better management and awareness of events associated with bone metastases.

1. Introduction

Metastatic disease in advanced cancer most commonly manifests itself in bone. Of all advanced breast or prostate cancer, 65% to 75% of patients develop metastases to bone, while in patients with other solid tumours 30% to 40% of patients will develop bone metastases [1]. Patients with bone metastases are at a high risk of developing SREs (such as bone pain requiring analgesics or palliative radiation therapy, spinal cord compressions (SCC), pathological fractures, hypercalcemia, or a need for surgery), which can greatly reduce quality of life (QOL) [3]. Retrospective analyses of several tumour types have demonstrated that patients with bone metastases who experience an SRE are more likely to experience subsequent SREs [2]. SREs undermine patients' functioning, beget significant morbidity, and reduce patients' survival. As treatment intent for patients with advanced cancers shifts from survival to the preservation of QOL, the principal objective becomes the management and prevention of SREs secondary to bone metastases.

"Skeletal-related complications" as a quantifiable clinical end point were first defined as pathologic fractures, irradiation of or surgery on bone, spinal cord compression, or hypercalcemia of malignancy (HCM); they were first applied to studies assessing pamidronate in women with bone metastases from breast cancer [3]. In the past, HCM 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. Therefore, in more recent studies, HCM has been excluded in the standard SRE definition. This is appropriate, as comparisons of HCM rates reported in studies performed in the 1990s show significantly lower rates of HCM than those conducted in the 1970s and 1980s [4]. In a retrospective analysis of patients with breast cancer from 1975 to 1984 who had first recurrence of disease in the bone, 17% developed hypercalcemia [5]. In the placebo arm of a study evaluating the safety of cyclic pamidronate in breast cancer patients, where study enrolment

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began in 1990, the incidence of hypercalcemia in patients with lytic bone disease was 13%, compared with 6% in the pamidronate arm [4].

The introduction of bone targeting agents to patients' treatment has been shown to be beneficial in preventing SREs and reducing pain in large phase III trials. Bone targeted therapies have been found to prolong the time to first SRE and reduce the rate of SREs [6]. The introduction of new anti-resorptive therapies into clinical practice, such as the nitrogen-containing IV bisphosphonate pamidronate early in the 1990s, zoledronic acid from 2000, and receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitor denosumab in 2010 is accompanied by increased disease state awareness. Consequently, general standards of care in the skeletal health of cancer patients have improved.

Nonetheless, SREs remain a common problem for patients with bone metastases from advanced cancer. As such, curtailing SREs will have benefits for the healthcare system in terms of reduced patient morbidity and lower healthcare costs [7]. The skeletal morbidity rate (SMR) is defined as the ratio of the number of SREs for each subject divided by the subject's time at risk in years. For example, if a study follows 1000 patients for one year and among those 1000 patients 350 SREs occur, then the SMR value would be 0.35 SREs/year. If multiple events are experienced within a year these values are included within the ratio.

This review aims to investigate how developments in bone targeted therapies have affected the incidence of SMRs over time. A trend analysis was performed to examine the SMR from the placebo arms of randomized controlled trials (RCTs) over time, and also the trend in the SMR values from the intervention arms of those RCTs over the same time period.

2. Methods

A literature search was conducted in MEDLINE (OvidSP) (1980 through September 2011), EMBASE (OvidSP) (1980 through September 2011), and Cochrane Central Register of Controlled Trials (OvidSP) (September 2011) 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". Those terms were then combined with the search terms for the following publication types and study designs: practice guidelines, systematic reviews, meta-analyses, reviews, randomized controlled trials, and controlled clinical trials. The literature search was not restricted by language. Studies were limited to phase III and IV trials involving patients with solid tumours, excluding trials in patients with multiple myeloma. Articles reporting the same population data were excluded.

Results of the search were independently sorted for potential inclusion by 6 coauthors. 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, spinal cord compression, surgical intervention and hypercalcemia. The articles were further refined, selecting only those that reported SMR. SMR values were the most consistently quoted outcome measure after SRE, in 14 of the 20 identified studies. The SMR was identified to be the primary outcome of interest in this study as it standardizes the rate of skeletal-related events over a time period, typically one year, where pure numerical events would unequally weigh trials to those with the longest follow-up or largest cohort.

As we were not privy to the median year of enrolment, for all selected studies, the mean enrolment year ([start of enrolment+end of enrolment]/2) was calculated. If these dates were unavailable, the corresponding authors or sponsoring companies were contacted. When all methods to gather this information were exhausted, for studies that did not report their enrolment period, the average of the mean enrolment year for the same intervention drug reported in literature was used. Here, an assumption was made that intervention drugs tend to be tested over approximately the same years. To normalize the distribution of SMR, natural log-transformation was applied. Graphs were created depicting SMR (log-scale) as a function of the year of enrolment for placebo arms and treatment arms. Due to the different enrolment numbers in each study, the SMR log-values were weighed accordingly (also known as weighted least squares). Weighted linear regression modified the standard linear regression model (minimizing the square of the error between predicted value $\hat{Y}_i$ and the actual value Y_i) to min $\sum_{i=1}^{m} W_i(Y_i-\hat{Y}_i)^2$, where W_i is the weighted value for each study (known as number of patients per study).These weighted linear regression models over time were constructed and p-values less than 0.05 were considered as statistically significance. Negative coefficients of time (slope) indicate that the average SMR (log-scale) is decreasing over enrolment year. The interaction term for the slopes of placebo versus intervention patients was calculated as well. We also conducted the above models with accounting for histology and/or drug as confounding factors due to heterogeneous studies. Histology was treated as a categorical variable with different primary cancer sites including breast, bladder, lung (other solid tumors), prostate, and renal cell carcinoma. For intervention treatment, different drug mechanism were accounted for, these included denosumab, ibandronate, pamidronate, and zoledronic acid. R^2 was calculated for each model, with higher values of the R^2 demonstrating better model fitting.

This process was repeated while considering histology as a confounding factor for both placebo and intervention arms. For patients treated with intervention, the different drugs used were also considered as a confounding factor. All analysis was conducted by Statistical Analysis Software (SAS version 9.2 for Windows).

3. Results

3.1. Analysis of SMR

A total of 14 studies were identified which reported SMR and the dates of enrolment (Table 1). The majority (7/14) included patients with breast cancer, three of the remaining involved patients with prostate cancer, two with renal cell carcinoma and a single study for each of primary bladder cancer and lung or other solid tumors. Enrolment periods for included studies ranged 17 years, from 1990 to 2007. Most studies identified compared zoledronic acid to placebo.

An overall downward trend was observed in the placebo arms of all studies using the natural log model of SMR (Fig. 1). In the early 1990s, SMRs ranging between 3.0 and 4.0 were not uncommon. After approximately a decade and a half, SMRs were reduced to around a single event per year. This trend was found to be statistically significant with a p-value of 0.0021 with a Pearson's correlation coefficient of 0.63.

During the same time period, statistically significant decreases in SMR were observed in all intervention arms included with a p-value less than 0.0001 with a R^2 of 0.64 (Fig. 2). At its peak in the early 1990s, SMRs ranged between 2.0 and 3.0. From the