Zoledronic acid treatment for cancerous bone metastases: a phase IV study in Taiwan

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Abstract

Aim of study: To investigate the features, adverse effects, bone marker changes in patients with breast cancer, prostate cancer, and multiple myeloma with bone metastases under Zometa® therapy.

Materials and Methods: This post-marketing study included 414 Taiwanese patients with bone metastases secondary to breast cancer, prostate cancer, or multiple myeloma who received Zometa® for 48 weeks. The patients’ characteristics, medication and adverse events were recorded, meanwhile changes in four serum bone metabolic markers and pain reduction were assessed every three months for one year.

Results: A total of 3,711 doses of Zometa® were infused, accounting for 294.5 patient-years. Adverse events occurred in 9.4% of patients, with bone pain, insomnia, constipation, and pyrexia as the most frequently reported. There was no osteonecrosis of the jaw. The incidence of skeletal-related events decreased significantly from 44.9% to 18.8%. Serum NTx, BAP, and TRACP5b steadily decreased to nadir at six months, but serum OPG was persistently elevated until the end of one year. The average decrease in pain score was 14.1, 14.3, and 16.7 for prostate cancer, breast cancer, and multiple myeloma patients, respectively.

Conclusion: Zometa® can be safely administered in Taiwanese patients with bone metastases secondary to breast cancer, prostate cancer, and multiple myeloma. There are concomitant decreases in skeletal-related events and bone pain.
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Introduction

Primary cancers spread to distant organs with characteristic preference, and the skeletal system is one of the most common sites. Breast and prostate cancer are osteotropic tumors. [1] Bone metastases are common causes of morbidity in 65-75% of patients with advanced breast or prostate cancer and in 70-95% of multiple myeloma patients. [2] Metastatic bone disease disrupts the normal bone homeostasis, resulting in increased and unbalanced bone metabolism, loss of bone integrity, and such skeletal morbidities including bone pain, hypercalcemia, pathologic fracture, and spinal cord or nerve root compression. All of these and their treatment may profoundly impair a patient's quality of life and eventually cause death. [3]

Despite developments in advanced cancer treatment in recent decades, skeletal morbidity remains a major clinical problem, with annual fracture rates of 20-40% and significant skeletal complications every three to six months in the absence of bone targeted therapies like bisphosphonates. [4] Bisphosphonates have become important components of treatment for tumor-associated osteolysis and hypercalcemia, Paget's disease, and the management of osteoporosis. [5] New-generation bisphosphonates, i.e., zoledronic acid (Zometa®), have clinical benefits for bone metastases secondary to solid tumors like prostate and breast cancers, and bone lesions from multiple myeloma.

Three phase III, randomized, double-blinded clinical trials demonstrated that Zometa® can safely and effectively reduce the incidence of skeletal complications associated with malignant bone disease. [6],[7],[8] Compared to placebo, the approved 4 mg dose reduced the risk of skeletal-related event (SRE) by 36%, 27%, and 28% in prostate cancer, non-small-cell lung cancer (NSCLC), and other solid tumors, respectively. In breast cancer and multiple myeloma, Zometa® reduced the risk of developing SREs by an additional 20% and 7%, respectively, compared to pamidronate. These findings set new standards of care and increased interest in identifying surrogate biological markers for monitoring the pathophysiology and progression of cancer in bone, whereas data of the placebo arm underscored the incidence and severity of skeletal morbidity in patients with bone metastases. [9]

The primary objective of this study was to evaluate the overall safety and SREs of a 48-week administration of Zometa® in Taiwanese patients with breast cancer, prostate cancer, and multiple...
myeloma, and changes in bone markers, specifically N-telopeptides of type 1 collagen (NTx), bone-specific alkaline phosphatase (BAP), osteoprotegerin (OPG), and tartrate-resistant acid phosphatase 5b (TRACP5b). [10],[11],[12]

Materials and Methods

Study design and patient population

This project was the first post-marketing, multi-center, open-labeled, prospective, observational study to evaluate the safety and side effects of Zometa®, as well as the occurrence rate of SREs after Zometa® treatment in Taiwanese patients. The study enrolled adult patients (age ≥20 years) with life expectancy greater than one year, an Eastern Cooperative Oncology Group performance status of 0 to 3 and objective evidence of bone metastasis by bone scan, radiographic studies, or biopsy, which were secondary to histologically- or cytologically-confirmed breast cancer, prostate cancer, or multiple myeloma. Patients were not eligible if they had corrected serum calcium level less than the lower limit of normal (LLN) at study entry; received bone radiation therapy three months prior to study entry; had abnormal renal function with a calculated creatinine clearance <30 ml/min using the Cockcroft-Gault formula; had evidence of severe cardiovascular disease, refractory hypertension, or symptomatic coronary artery disease six months prior to study entry; received intravenous bisphosphonates at study entry; had active dental problems including infection of the teeth or jaw bone (maxilla or mandible), dental or fixture trauma; had current or prior diagnosis of osteonecrosis of the jaw (ONJ), of exposed bone in the mouth, or of slow healing after dental procedures (six weeks before enrolment), or planned dental or jaw surgery (e.g., extraction, implants) during study period; and female patients of child-bearing potential but without adequate contraception, or those who were pregnant or breast-feeding. The Institutional Review Board of all centers reviewed and approved the study design and all patients provided written informed consent. This trial was conducted in accordance with the good clinical practice and the Declaration of Helsinki.

Zometa®, a third-generation highly potent bisphosphonate containing two nitrogens, was investigated in this study. [13],[14],[15] All patients who had fulfilled the inclusion criteria received Zometa® for 48 weeks. For patients with baseline creatinine clearance (Ccr) >60 mL/min, the recommended dose was 4 mg as a single intravenous infusion for more than 15 min every three-to-four weeks. The dose was reduced to 3.5 mg, if the Ccr was 50-60 mL/min; 3.3 mg if Ccr was 40-49 mL/min; 3.0 mg if Ccr was 30-39 mL/min. The first patient was enrolled in December 2005 and the last patient in December 2006, whose last visit was in December 2007.

The primary objective was to evaluate the safety of patients during the 48-week Zometa® treatment period. Safety assessment was based mainly on the frequency of adverse events (AE), including all serious adverse events (SAE), SREs, and/or ONJ. A SRE was defined as any event involving radiation therapy to bone, bone surgery, pathologic fracture, spinal cord compression, change of anti-neoplastic therapy to treat bone pain, and hypercalcemia of malignancy (HCM). The condition of ONJ was defined as a vascular necrosis resulting from impaired blood supply to the bone, not usually associated with infection, and clinically diagnosed by exposed bone in the maxilla-facial area, poor wound healing, and pain for at least 8 weeks. [16] All cases of SRE, ONJ, and osteomyelitis were reported as SAEs in this study as the protocol specified. Hematology and biochemistry assessment, except creatinine, were performed at baseline and at the study end. Serum creatinine was evaluated on each scheduled visit and was monitored for safety concerns. Dose modification or delayed dosing in the next treatment was implemented for elevated serum creatinine above baseline values.

http://www.cancerjournal.net/printarticle.asp?issn=0973-1482;year=20...
Four serum bone metabolic markers, including NTx, BAP, OPG, and TRACP5b, were measured every 3 months for one year. Serum NTx and BAP were measured in all cases. The TRACP5b and OPG were measured in selective sites in Northern Taiwan only. Single-sample t-test was used to perform intra-group comparison using the baseline value as reference. These markers were performed at baseline and every 3 months for one year. Bone markers were centrally assessed in the Special Hematology Laboratory of TSGH in Northern Taiwan and by the Union Clinical Laboratory (UCL) in central and southern Taiwan according to previously established methods. [12] Specimen collection, storage, and shipment were conducted in accordance with the standard operation procedures provided by the laboratory.

Bone pain was measured by visual analogue scale (VAS; 0-100 mm) every 3 months for one year in each individual patient.

Statistical methods

The safety, changes of bone markers, and bone pain reduction of patients given Zometa® were evaluated and calculated. There were three sub-groups according to the individual disease types, i.e. breast cancer, prostate cancer, and multiple myeloma. Exploratory analyses were performed using descriptive statistics. Each sub-group was tested for within group differences but no comparison between sub-groups was made. All statistical analyses were 2-sided with 0.05 level of significance.

Data from all study centers was pooled for central analysis. The percent change from baseline of bone markers was analyzed within each individual group. The geometric means and two-sided 95% CIs of absolute values and changes in each serum biochemical level at every three-month interval were calculated. Single-sample t-test was used to perform intra-group comparison using the baseline value as reference.

Results

A total of 414 Taiwanese patients were enrolled in 31 centers from October 18, 2005 to December 29, 2006, and the study was completed on February 28, 2008. Their demographics and baseline disease characteristics were summarized in [Table 1]. Two hundred and ten patients (50.7%) completed the study, while 204 (49.3%) did not. The most common reasons for discontinuation were death (17.1%) and consent withdrawal (16.9%). An overview of the disposition of the patient population and summary of patients who discontinued the study were shown in [Table 2]. {Table 1}{Table 2}

A total of 3,711 doses were infused, accounting for 294.5 patient-years (about 12-to-13 doses per patient-year) for all trial subjects. These were divided into 166. One patient-year with 2,126 doses for the breast cancer group, 111.1 patient-year with 1384 doses for the prostate cancer group, and 17.3 patient-year with 201 doses for the multiple myeloma group. Of the trial subjects, 92.5% received the maximum dosage of 4.0 mg Zometa®, 94.3% in the breast cancer group, 90.2% in the prostate cancer group, and 89.1% in the multiple myeloma group. In the breast cancer group, 5.3% received 3.0~3.9 mg and 0.4% received 1.5~2.9 mg. In the prostate cancer patients, 8.2% received 3.0~3.9 mg and 1.6% received 1.5~2.9 mg, while in the myeloma patients, 10.9% received 3.0~3.9 mg and none received 1.5~2.9 mg. During the study period, the median exposure time to Zometa® was 11.1 months and a median of 11.0 doses in the breast cancer group, 11.0 months and 10.0 doses, respectively, in the prostate cancer group, and 9.9 months and 8.0 doses, respectively, in the multiple myeloma group.

Bone pain, insomnia, constipation, and pyrexia were the most frequently reported adverse events.
Zometa®-related adverse events occurred in 39 of 414 participants (9.4%), including pyrexia, hypocalcemia, vomiting, nausea, headache, bone pain, skin rash, edema, hypo-aesthesia, and elevated blood creatinine. Most of these adverse events were mild and moderate, with only 4 severe cases reported. There was no ONJ reported. The number of patients with each type of SRE that occurred before study entry and during the study were summarized in [Table 3] and [Table 4]. Of the 414 cancer patients, 186 (44.9%) experienced at least one SRE before entering the study. During the study period, the proportion of patients who experienced at least one SRE was reduced to 18.8% (78 patients). This trend was consistent with breast cancer, from 48% (107 patients) down to 21.1% (47 patients), prostate cancer, from 37.2% (61 patients) down to 15.2% (25 patients), and multiple myeloma, from 66.7% (18 patients) down to 22.2% (6 patients). The most frequently seen SRE during the study was radiotherapy to the bone, which accounted for 8.2% of cases. The second was pathologic fracture, which accounted for 6.8%, followed by change of anti-neoplastic therapy to treat bone pain (3.4%), spinal cord compression (1.9%), bone surgery (0.7%), and HCM (0.2%). As regards individual type of cancers during the study, the occurrence rate of different SRE was similar. In the breast cancer group, 9.9% of subjects experienced radiation therapy to the bone, 5.8% had pathologic fracture, 5.4% changed their anti-neoplastic therapy to treat bone pain, 1.8% experienced spinal cord compression, and 0.4% each had bone surgery and HCM. Among the prostate cancer patients, 6.7% experienced pathologic fracture, 6.1% had radiation therapy to the bone, and 1.2% each had a change of anti-neoplastic therapy, spinal cord compression, and bone surgery. For the multiple myeloma group, 14.8% had pathologic fracture and 7.4% each had radiation therapy to the bone and spinal cord compression, and none had change of anti-neoplastic therapy, bone surgery, or HCM.

Four serum bone metabolic markers, including NTx, BAP, OPG, and TRACP5b were measured every 3 months for 1 year [Figure 1]. Serum NTx and BAP were measured in 387 cases while TRACP5b and OPG were measured in 100 cases in selective sites of Northern Taiwan only. The measured mean level of serum NTx at baseline was 19.70 nmol BCE (95% CI: 18.06–21.50 nmol BCE), while that at 3 months was 16.09 U/L (95% CI: 14.90–17.37 U/L). There was a sustained downward trend overall and for each individual cancer group. After one year follow-up, the serum NTx level decreased to 67.83% of baseline value overall, and to 70.80% in the breast cancer group, 65.12% in the prostate cancer group, and 60.92% in the multiple myeloma group. Intra-group comparison revealed significant change in all post-baseline time points in serum NTx levels for the breast cancer and prostate cancer groups. However, no significant changes were detected during the first 9 months of therapy for the multiple myeloma group, but serum NTx levels significantly decreased after one year of Zometa®. The measured mean level of serum BAP at baseline was 47.97 U/L (95% CI: 43.72–52.63 U/L), and 44.41 U/L (95% CI: 40.53–48.67 U/L) at 3 months. There was sustained downward trend overall and for each individual cancer group. After one-year follow-up, serum BAP level decreased to 70.29% of baseline value overall, and to 74.17%, 63.81%, and 85.18% in the breast cancer group, prostate cancer group, and multiple myeloma group, respectively. Intra-group comparison using single-sample t-test revealed significant change in all post-baseline time points in serum NTx levels for the breast cancer and prostate cancer groups. However, no significant changes were detected during the first 9 months of therapy for the multiple myeloma group, but serum NTx levels significantly decreased after one year of Zometa®. The measured mean level of serum BAP at baseline was 47.97 U/L (95% CI: 43.72–52.63 U/L), and 44.41 U/L (95% CI: 40.53–48.67 U/L) at 3 months. There was sustained downward trend overall and for each individual cancer group. After one-year follow-up, serum BAP level decreased to 70.29% of baseline value overall, and to 74.17%, 63.81%, and 85.18% in the breast cancer group, prostate cancer group, and multiple myeloma group, respectively. Intra-group comparison using single-sample t-test revealed significant change in all post-baseline time points in serum NTx levels for the breast cancer and prostate cancer groups, but not in the multiple myeloma group. In all cancer groups, the mean baseline OPG level was 691.26 pg/mL (95% CI: 625.20–764.29 pg/mL), which was 733.70 pg/mL (95% CI: 671.53–801.63 pg/mL) at month six. The sustained upward trend was apparent for the prostate and breast cancer groups. After one year follow-up, the OPG level increased to 158.63% of baseline in the prostate cancer group and 124.49% in the breast cancer group. The statistically significant increase was noted after nine months of Zometa® in the breast and prostate cancer groups. During the first 6 months of therapy, there was a significant decrease in TRACP 5b level in both the breast and prostate cancer groups. After that, the TRACP 5b levels increased towards baseline level. After 12 months of Zometa®, the TRAP 5b returned to baseline level for the prostate cancer patients, but only 85.72% of baseline in the breast cancer group. [Figure 1]

Absolute and changes of pain VAS at every three-month interval were calculated. Single-sample t-test was used to perform intra-group comparison using the baseline value as reference standard. The results
were shown in [Figure 2]. At baseline, the bone pain scores were 47.5, 43.4, and 42.8 for the prostate cancer group, breast cancer group, and multiple myeloma group, respectively. After 12 months of Zometa®, the average decrease of pain score was 14.1 for prostate cancer patients, 14.3 for breast cancer patients, and 16.7 for multiple myeloma patients.[Figure 2]

Discussion

This post-marketing study examined the safety of Zometa® in 414 Taiwanese patients of breast cancer, prostate cancer, and multiple myeloma with bone metastases. Zometa® can be safely given with good tolerability as administered intravenously over at least 15 min. [13] The incidence of Zometa®-related adverse events is less than 10%. Pyrexia (4.1%) is the most frequently encountered side effect, followed by hypocalcemia (1.2%), which are consistent with previous reports. [14] Surprisingly, bone pain is not considered a side effect of Zometa® by the investigators, although it is recorded as the most common adverse event in this study. That is probably because most of the investigators were not aware that bone pain can be caused by Zometa® when this study was being conducted.

Another noteworthy side effect of Zometa® is renal function impairment. In this study, clearance of serum creatinine is used as a surrogate measure of renal function. There is impairment of renal function in breast cancer and prostate cancer patients when Zometa® is instituted for one year. Although, renal function improves in myeloma patients after Zometa® treatment, the patient number is insufficient to make a definitive conclusion that Zometa® can be beneficial in this regard.

Osteonecrosis of the jaw (ONJ) is a serious complication of bisphosphonates that has received much attention since 2003. It is often diagnosed by the criteria of a lack of healing following 6-8 weeks of appropriate dental care in the absence of osteoradionecrosis or metastatic disease to the jaw, although no uniform diagnostic criteria has been established. The etiology and pathogenesis remain unclear. However, it is likely to be multi-factorial, including oral infection, inflammation, oral surgery, poor dental hygiene, alcohol abuse, or concomitant radiation or chemotherapy. [16],[17],[18] It tends to occur with long exposures to bisphosphonates. In the largest retrospective study from the MD Anderson Cancer Center involving 4,000 patients who received intravenous bisphosphonates, the frequency of ONJ was 0.85%. [17] Patients with ONJ have longer duration of disease and receive greater doses of bisphosphonate therapy than patients without ONJ. [16],[17] In previous literatures, the median time to the occurrence of ONJ after the use of zoledrionic acid in cancer patients with bony metastases ranged from 8.9 months to 1.38 years. [19],[20],[21] In our study, we did not observe any case of ONJ. It could be due to the short study period, well educating patients to prevent dentoalveolar surgery and improve oral hygiene, geographic variance of ONJ incidence, or just by chance. [19],[20],[21]

Before entering this study, 44.9% of the 414 patients had experienced at least one SRE. During the study period, the proportion of patients with at least one SRE was 18.8% (78 patients). The incidence of SRE decreased significantly after Zometa® was started. The most frequent reported adverse events are radiotherapy to the bone, pathologic fracture, and spinal cord compression among the three patient groups. The trend of less SRE after Zometa® treatment is obvious.

Two methodologies have been used in this study to measure the efficacy of Zometa® treatment on bone metastases, i.e. pain VAS and serum bone biochemical marker assays. Pain assessment by VAS is more subjective and serum bone biochemical marker assays are more objective. For the three tumor types evaluated in this study, the pain VAS changes indicate that Zometa® can lead to statistically significant decrease in bone pain. Generally, the pain score decreases from 44.7 at baseline to 28.0 after one year of
follow-up.

Four bone biochemical markers have been measured, including two bone resorption markers (NTX and TRACP5b), one bone formation marker (BAP), and OPG. Serum NTx, BAP, and TRACP5b steadily decrease to nadir at 6 months after start of Zometa®. However, serum OPG is persistently elevated until the end of one year. Similar results have been reported in some studies. [22],[23] The results of these two methodologies are quite consistent, indicating the efficacy of Zometa® in treating metastatic bone disease from different cancer types.

In conclusion, this post-marketing study of Zometa® treatment demonstrates that it can be safely administered in Taiwanese patients. Its efficacy is evidenced by the suppression of serum bone biochemical markers, decreased risk of skeletal-related events, and reduced bone pain in prostate cancer, breast cancer, and multiple myeloma patients with bone metastases.

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