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# EORTC QLQ-BM22 Quality of Life Evaluation and Pain Outcome in Patients with Bone Metastases from Breast Cancer Treated with Zoledronic Acid

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**Abstract.** *Background: We assessed the effect of zoledronic acid on quality of life (QOL) and pain outcome in breast cancer patients with bone metastases using the European Organization for Research and Treatment of Cancer bone metastases module (EORTC QLQ-BM22). Patients and Methods: Three hundred sixty-six breast cancer patients receiving zoledronic acid for bone metastases from 13 Centers were prospectively enrolled. QOL was evaluated using the EORTC QLQ-BM22 and pain outcome were measured monthly with a Visual Analog Scale (VAS) score for 24 months. Results: No significant change of functional scale (functional interference and psychosocial aspects) of the EORTC QLQ-BM22 was reported. Significant reduction of the symptom scale was noted after treatment compared with the baseline. The painful site subscale was significantly reduced during the first 12 months, with the exception the 6-month follow-up of point. Pain characteristics subscale was also significantly lower from the 2-month time point onwards. VAS scores indicated a significant reduction in pain over the course of the study to the 22-month time point follow-up compared to the baseline. Conclusion: Zoledronic acid treatment improved QOL of breast cancer patients with bone metastases by relieving bone pain.*

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*Key Words:* Zoledronic acid, breast cancer, bone metastases, quality of life, pain.

Breast cancer is the most frequently-diagnosed cancer and the leading cause of cancer death in females worldwide (1). Bone is the most common site for metastasis in breast cancer, and patients with advanced breast cancer are at high risk for developing bone metastases and experience skeletal complications (2, 3). Patients with bone metastases often develop moderate to severe pain which significantly decreases functionality and quality of life (QOL) (4, 5). Therefore, delaying the onset and/or reducing pain associated

Table I. *Baseline patients' characteristics (N=366).*

| Characteristic | N (%) |
|---|---|
| Age (Mean ± SD) | 53.7±11.0 |
| Number of bone lesion(s) | |
| 1 | 91 (24.9%) |
| 2-5 | 169 (46.2%) |
| >5 | 106 (29.0%) |
| Type of bone metastasis | |
| Sclerotic | 53 (14.5%) |
| Lytic | 117 (32.0%) |
| Mixed | 113 (30.9%) |
| Unclassified | 83 (22.7%) |
| ECOG performance status | |
| 0 | 219 (59.8%) |
| 1 | 125 (34.2%) |
| 2 | 22 (6.0%) |

ECOG: Eastern Cooperative Oncology Group.

with bone metastases is an important goal in the palliative treatment of patients with bone metastases from breast cancer.

Zoledronic acid, a bisphosphonate that potently inhibiting osteoclastic activity, has been shown to significantly reduce the overall risk of skeletal complications and provide durable pain reduction in patients with bone metastases from breast cancer (5-7). Zoledronic acid treatment improves QOL, a primary goal of treatment in palliative oncology as it constitutes the international standard for patients with bone metastases from breast cancer.

Herein, we report the effect of zoledronic acid on QOL assessed through the use of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire for Patients with Bone Metastases (EORTC QLQ-BM22) and pain outcome in women with breast cancer metastatic to bone during the first 24 months of treatment.

## Patients and Methods

*Patients*. This phase IV, single-arm, non-comparative, open label, and observational study was conducted across 13 medical centers in Taiwan between July 2008 and November 2012. A total of 366 breast cancer patients with bone metastases who underwent zoledronic acid treatment according to standard of care under the supervision of the treating physician were enrolled in this study. As a standard of care, patients received 4 mg of zoledronic acid *via* 15-min intravenous infusion every month for up to 24 months. Inclusion criteria were as follows: female >20 years of age with histologically or cytologically confirmed diagnosis of breast cancer and radiological evidence of one or more bone metastases. Exclusion criteria included radiotherapy to bone within three months prior to study and prior treatment with bisphosphonates. Pregnant and lactating females were also excluded. The study was approved by the Institutional Review Boards or Ethics Committee for each site and all patients provided written informed consent prior to enrollment.

*Quality of life assessment with EORTC QLQ-BM22*. The 22-item EORTC QLQ-BM22 questionnaire assesses disease symptoms related to bone metastases. It contains four subscales: painful sites and pain characteristics on the symptom scale and functional interference and psychosocial aspects on the functional scale. All items were scaled from 1 (not at all) to 4 (very much), in which a higher score indicates greater distress in symptom scales while a higher score in functional scale indicates greater functional ability. Each scale was converted to a score ranging from 0 to 100.

*Pain assessment*. A horizontal Visual Analog Scale (VAS), ranged from 0 to 100 millimeter (mm), anchored by word descriptors at each end was used for patients' self-assessment of pain. The patient marked on the line the point that they felt represented their perception of their current state. The VAS score was determined by measuring from the left hand end of the line to the point that the patient marks.

*Statistical analysis*. A change of score from baseline of more than 10% as analyzed by longitudinal data with mixed model was considered clinically significant. All statistical tests were performed using a two-sided test at the 5% significance level.

## Results

Table I lists the baseline characteristics of the 366 patients. The median time between first breast cancer diagnosis and bone metastases was 3.7 years. Patients were diagnosed with bone metastases of a median of 5.4 months before zoledronic acid treatment.

Table II shows the number of patients which completed the EORTC QLQ-BM22 questionnaire and the results. The mean baseline value of the two functional subscales, functional interference and psychosocial aspects, were 69.2 and 59.7, respectively. No significant change in these two functional subscales was observed throughout the study period. Significant reduction of symptom scale, however, was noted after treatment compared with the baseline. With the exception of the 6-month follow-up point, painful site subscale decreased significantly during the first 12 months. Significantly decreased pain characteristics subscale was also reported by patients from the 2-month time-point onwards compared with the baseline.

Bone pain was measured from 0 mm to 100 mm according to a VAS (Table III). The mean pain VAS score was 35.5 mm at baseline and decreased significantly over the course of the study to the 22-month time point follow-up. The reduction of VAS pain score after the administration of zoledronic acid was in agreement with the decreased pain characteristics subscale in the EORTC QLQ-BM22.

## Discussion

Breast cancer metastatic to bone results in intractable bone pain and skeletal morbidities that negatively impact patients'

Table II. *EORTC QLQ-BM22 subscale scores from time of baseline to different time points.*

| | Baseline | 2 months | 4 months | 6 months | 8 months | 10 months | 12 months | 14 months | 16 months | 18 months | 20 months | 22 months | 24 months |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Patients completed questionnaire | 366 | 347 | 322 | 307 | 276 | 263 | 245 | 229 | 210 | 192 | 183 | 166 | 153 |
| Functional interference | 69.2±1.2 | 74.2±1.2 | 74.8±1.2 | 74.8±1.3 | 76.0±1.3 | 75.7±1.4 | 76.1±1.4 | 74.8±1.4 | 75.5±1.5 | 76.0±1.6 | 75.1±1.6 | 75.3±1.7 | 72.7±1.8 |
| Psychosocial aspects | 59.7±0.9 | 60.5±0.9 | 59.9±0.9 | 60.5±1.0 | 60.1±1.0 | 59.9±1.0 | 60.0±1.1 | 59.5±1.1 | 59.5±1.1 | 58.8±1.2 | 59.4±1.2 | 58.9±1.3 | 58.2±1.3 |
| Painful site | 25.2±1.0 | 22.5±1.0* | 22.5±1.1* | 22.6±1.1 | 22.0±1.1* | 21.8±1.2* | 22.0±1.2* | 22.5±1.3 | 22.9±1.3 | 23.4±1.4 | 23.8±1.4 | 24.5±1.5 | 24.7±1.5 |
| Pain characteristics | 27.3±1.1 | 22.3±1.2* | 20.1±1.2* | 21.1±1.2* | 20.1±1.3* | 19.9±1.3* | 20.0±1.4* | 20.3±1.4* | 20.8±1.5* | 20.4±1.5* | 21.9±1.6* | 21.1±1.6* | 23.0±1.7* |

Scores are expressed as mean±standard error; *change form baseline >10% and $p<0.05$; *p*-values denote the significance of difference between each time point and baseline.

Table III. *Visual Analog Scale (VAS) scores from time of baseline to different time points.*

| | Baseline | 2 months | 4 months | 6 months | 8 months | 10 months | 12 months | 14 months | 16 months | 18 months | 20 months | 22 months | 24 months |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Patients assessed | 362 | 339 | 312 | 290 | 269 | 253 | 235 | 213 | 190 | 178 | 162 | 142 | 113 |
| VAS scores | 35.5±1.5 | 27.6±1.5* | 28.0±1.5* | 29.7±1.6* | 30.3±1.6* | 29.2±1.6* | 29.7±1.6* | 30.8±1.7* | 31.7±1.7* | 30.5±1.8* | 29.4±1.8* | 31.8±1.9* | 35.5±2.1 |
| Change | –- | –22.4% | –21.0% | –16.4% | –14.5% | –17.8% | –16.4% | –13.3% | –10.7% | –13.9% | –17.1% | –10.3% | 0.0% |

VAS scores are expressed as mean±standard error; *$p<0.05$; *p*-values denote the significance of difference between each time point and baseline.

QOL. Zoledronic acid treatment improves the QOL of patients by preventing skeletal complications and providing relief from bone pain, and is the standard-of-care for breast cancer patients with bone metastases (8-10). In a double-blind, randomized, placebo-controlled trial that involved 228 Japanese patients with bone metastases from breast cancer, the zoledronic acid-treated group showed statistically significant improvement in pain scores, which were consistently below baseline, at 4 weeks and at every subsequent time point during the study, when compared to placebo (8).

The present study was designed to determine the effect of zoledronic acid on the QOL of breast cancer patients with bone metastases in the aspect of pain management. QOL is most frequently addressed and measured in clinical trials by use of a core measure questionnaire such as the EORTC QLQ-C30. The present study used the EORTC QLQ-BM22 that was designed to address issues relating to bone metastases (11). The EORTC QLQ-BM22 results showed that despite no improvement of functional scale (functional interference and psychosocial aspects) was reported, significant reduction of symptom scale was observed after treatment compared to baseline. Painful site subscale decreased during the first 12 months and pain characteristics subscale was significantly lower from the 2-month time point onwards compared to baseline.

Results of the 24-month analysis of patient self-assessment of bone pain by using the VAS score indicate that breast cancer patients metastatic to the bone experienced clinically significant levels of pain relief throughout the course of the treatment. This findings is consistent with the findings of symptom scale of the EORTC QLQ-BM22.

A potential limitation to this study design is that pain assessment was subjective and conducted at fixed time points a month apart which may not reflect all experiences of pain associated with the disease. Other limitations of the study included the lack of control arm or placebo. In summary, given the demonstrated bone pain-relieving efficacy of zoledronic acid, this phase IV, prospective, and observational study has confirmed the significant clinical benefits of zoledronic acid in patients with bone metastases secondary to breast cancer with EORTC QLQ-BM22.

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## Conflicts of Interest

The Authors have declared that no competing interests exist.

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