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Research Article

Effects of de-escalated bisphosphonate therapy on the Functional Assessment of Cancer Therapy-Bone Pain, Brief Pain Inventory and bone biomarkers

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ABSTRACT

Background: The Brief Pain Inventory (BPI) and Functional Assessment of Cancer Therapy-Bone Pain (FACT-BP) are commonly used measures of patient reported pain outcomes. We report on the performance of the FACT-BP in comparison to the BPI within a small, randomized trial.
Methods: Patients with biochemically defined low risk bone metastases were randomized to 4 weekly (control arm) or 12 weekly (de-escalating arm) pamidronate for 1 year. FACT-BP, BPI and serum markers of bone turnover were recorded at baseline and weeks 12, 24, 36 and 48. Mixed effects models were used to compare scores over time between arms. Correlation coefficients were calculated to evaluate the association between FACT-BP and BPI scores, as well as with markers of bone turnover.
Results: Nineteen patients were randomized to each study arm. Pain scores determined by the two instruments were moderately to highly correlated with each other. Baseline C-telopeptide (CTx) level was correlated with baseline FACT-BP and BPI scores. Baseline bone-specific alkaline phosphatase showed a non-significant association with pain scores. There were no correlations between the markers of bone turnover and pain scores at week 12.
Conclusions: In the current study the FACT-BP and BPI correlated well with each other, and with baseline CTx. The possibility of linking subjective pain scores with objective biomarkers of response requires more investigation.

1. Introduction

Bone pain is a common symptom in patients with metastatic disease and can be severe, debilitating, and significantly interfere with a patient's quality of life. It is therefore important to develop validated measures of patient-reported outcomes such as, bone pain, impact on daily activities, and quality of life (QoL) to evaluate the efficacy of both anti-cancer drugs and bone-targeted agents [1]. The method of obtaining these measures also needs to be practical to allow for routine use in the clinic [2,3].

One of the most commonly used tools to assess pain is the Brief Pain Inventory (BPI) that was developed by the Pain Research Group of the WHO Collaborating Center for Symptom Evaluation in Cancer Care. BPI consists of 11 questions designed to assess pain location, severity, relief and interference [4]. The Functional Assessment of Cancer Therapy-Bone Pain (FACT-BP) [5] was developed to specifically assess cancer-related bone pain and its effects on patient QoL. The FACT-BP is a 16-item scale. Fifteen of the items are used to calculate a summed score, with higher aggregate scores representing less bone pain, or better QoL. After its initial launch, the questionnaire was subsequently modified and currently two versions exist: the 16-item version and a 20-item version that includes minor rewording of five items and a more detailed assessment of the impact of pain on daily functioning [6] (Table 1).

The 16-item version was evaluated in two prospective phase II trials of similar design in which less potent bisphosphonates were switched to a third-generation bisphosphonate (zoledronic acid in one and ibandronate in other study) [5]. FACT-BP has been shown to be a robust and concise tool for assessing cancer-related bone pain in addition to the impact of that pain upon functioning and QoL [5].

We have recently completed a prospective randomized feasibility study of de-escalated bisphosphonate treatment with

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Table 1
Items included in the 16- and 20-item versions of the FACT-BP.

		16-item version [6,9]	**20-item version** [10]
GF7	I am content with the quality of my life right now	X	X
P2	I have certain parts of my body where I experience <significant> pain	X	X
BP1	I have bone pain	X	X
BP2	It hurts when I put weight or pressure on the place where I have bone pain	X	X
BP3/BP21	I have bone pain even when I sit <or lie> still	X	X
BP4	I need help doing my usual activities because of bone pain	X	X
BP5	I am forced to rest during the day <because of/due to> bone pain	X	X
BP6	I have trouble walking because of bone pain	X	X
BP7	Bone pain interferes with my ability to care for myself (bathing, dressing, eating, etc.)	X	X
BP8	Bone pain interferes with my social activities	X	X
BP9/ BP18	Bone pain <wakes me up at night / interferes with my sleep>	X	X
BP10	I am frustrated by my bone pain	X	X
BP11	I feel depressed about my bone pain	X	X
BP12	I worry that my bone pain will get worse	X	X
BP13	My <family has trouble understanding when my> bone pain interferes with my <activity/family life>	X	X
BP14	Bone pain interferes with my ability to do vigorous activity (exercise, heavy lifting, etc.)		X
BP15	I have trouble concentrating due to my bone pain		X
BP16	I have difficulty coping with my bone pain		X
BP17	I have difficulty working due to my bone pain (including work at home)		X
Q7	In how many places in your body have you felt bone pain?	X	X

Wording differences between versions are indicated by< >.

intravenous pamidronate in patients with metastatic breast cancer to bone [7]. Here we report on an analysis utilizing data from this trial aimed at comparing BPI and FACT-BP and to correlate these with bone turnover markers.

2. Methods

We utilized data from a randomized, non-inferiority feasibility trial conducted in a single large cancer center [7]. The trial enrolled women with breast cancer and radiological or biopsy confirmed bone metastases with bone turnover marker C-telopeptide (CTx) levels in the low-risk range (defined as serum CTx levels in the lowest tertile [< 600 ng/L]). Eligible patients were stratified according to baseline serum CTx (< 400 ng/L and 400–600 ng/L) and duration of prior bisphosphonate use (< 6 months and > 6 months) and were then randomly allocated to receive 90 mg pamidronate intravenously every 3–4 weeks (control group) or every 12 weeks (de-escalated group). Serum was collected from enrolled patients following an overnight fast at baseline and weeks 12, 24, 36 and 48. Patients also completed the BPI and the 16-item version of FACT-BP at the same times at baseline, and weeks 12, 24, 36 and 48. Those remaining in the low-risk CTx group continued to receive their allocated treatment. Those whose CTx levels rose above 600 ng/L remained on study, but thereafter received treatment every 3–4 weeks. Censoring was carried out for any patient receiving radiation therapy to bone or a change in systemic therapy. The trial was approved by the respective institutional Research Ethic Board.

Data on cumulative scores for both BPI and FACT-BP have been reported elsewhere [7]. Here, we also assessed item-level scores such as average pain over the past 7 days, worst pain over the past 7 days, and pain right now.

2.1. Bone turnover marker analysis

At baseline and various times on treatment, serum samples were obtained and analyzed for levels of the bone turnover markers CTx and BSAP using specific enzyme linked immunosorbent assay (ELISA). The threshold of sensitivity for CTx was ~10 ng/L (Beta-Cross Laps/Serum Assay, Roche Diagnostics Canada Inc.), while it was 0.7 IU/L for BSAP (Metra Biosystems, San Diego CA).

Table 2
Number of patients who completed FACT-BP and BPI at each time point on study. Adapted from [11].

Week on study	Number of patients
0	29
12	22
24	18
36	14
48	11

2.2. Statistical analysis

A mixed effects model for repeated measures was used to compare scores over time between treatment arms. An unstructured covariance pattern was used to account for the correlations within patients. The model included fixed effects (treatment arm, time [measured in weeks], and a treatment × time interaction term) and random effects (patient, patient × time). Pearson correlation coefficients were calculated to evaluate the association between FACT-BP and BPI scores, along with the association of FACT-BP and BPI scores with levels of bone turnover markers at baseline and week 12 time points.

3. Results

A total of 38 patients were randomized with 19 patients in each arm, and 29 patients completed FACT-BP and BPI at baseline. At week 12, data was available for correlation of pain scores with bone turnover marker levels for 22 patients, 11 patients completed questionnaires at week 48 (Table 2).

3.1. Correlation between BPI and FACT-BP

Results of the FACT-BP scores at each time point for patients in the study are plotted by treatment arm in Fig. 1. Using a mixed effects model, the trend in pain scores over time did not significantly differ between groups ($p=0.386$). Similarly, there were no differences in trends between treatment arms in the BPI ratings of average pain ($p=0.164$), worst pain ($p=0.297$), and pain right