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.

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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
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 (con-
trol 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 week 12 time points. Baseline and week 12 data was
available for correlation of pain scores with bone turnover markers
at baseline and week 12 time points.

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).

2.2. Statistical analysis

A mixed effects model for repeated measures was used to
compare scores over time between treatment arms. An unstruc-
tured 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 corre-
lation 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 signi-
cantly 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

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Table 1

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

| Item | 16-item version [6,9] | 20-item version [10] |
|------|----------------------|---------------------|
| GF7  | X                    |                     |
| P2   | X                    |                     |
| BP1  | X                    |                     |
| BP2  | X                    |                     |
| BP3/BP21 | X                  |                     |
| BP4  | X                    |                     |
| BP5  | X                    |                     |
| BP6  | X                    |                     |
| BP7  | X                    |                     |
| BP8  | X                    |                     |
| BP9/ BP18 | X                |                     |
| BP10 | X                    |                     |
| BP11 | X                    |                     |
| BP12 | X                    |                     |
| BP13 | X                    |                     |
| BP14 | X                    |                     |
| BP15 | X                    |                     |
| BP16 | X                    |                     |
| BP17 | X                    |                     |
| Q7   | X                    |                     |

Wording differences between versions are indicated by < >.

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Table 2

Number of patients who completed FACT-BP and BPI at each time point on study.

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

Adapted from [11].
now ($p = 0.234$). Correlations between the FACT-BP and BPI scores were moderate to strong. Specifically, at baseline in the combined sample, the Pearson correlation coefficient between the FACT-BP with BPI worst pain was $0.70$, with BPI average pain was $0.45$, and with BPI pain right now was $-0.57$.

### 3.2. Correlation between pain scores and bone turnover markers

Pearson’s correlation coefficients and associated $p$-values are shown in Table 3. Significant correlations were observed between levels of CTx and pain scores as assessed by FACT-BP ($r = 0.487$ and $p = 0.006$) or BPI ($r = 0.491$ and $p = 0.006$) at baseline, however no significant correlations were observed with similar measures taken at week 12 on study. BSAP at baseline was also significantly correlated with pain scores assessed by FACT-BP ($r = 0.363$ and $p = 0.05$), and trended with baseline pain scores as determined by BPI ($r = 0.329$ and $p = 0.08$). No significant correlations were observed for BSAP with pain assessed by either tool at the 12 week time point (all $r < 0.20$).

### 4. Conclusion

Despite skeletal morbidity being associated with reduced quality of life and shortened survival, a reduction in the rate of skeletal related events (SREs) with bone-targeted agents has not shown any improvement in global quality of life scores or survival [8–12]. This raises a question regarding the sole use of SREs as clinically relevant endpoints. Bone pain is usually the earliest and most common symptom in patients developing skeletal metastases. Patient-reported bone pain reflects an individual patient’s experience regarding pain severity and its impact on functioning and QoL. Bone pain is a logical candidate for evaluating treatment efficacy. Several groups have therefore been developing scores that are meaningful, valid, easy and fast to complete and assess.

Matza and colleagues measured bone pain in oncology trials, and concluded that most approaches used simple assessment of general bodily pain, often with single items [2]. They recommended that bone pain assessment tools be validated within the target population (i.e., people with bone pain), and have sufficient content validity to represent the important concerns and specific impact of this unique pain experience. The Functional Assessment of Cancer Therapy-Bone Pain (FACT-BP) was developed in 2004 and published in 2009 [5], to provide such a tool. Similarly, others have tried to link biomarkers of bone turnover with a range of other pertinent surrogates [13].

The objectives of this study were to evaluate the performance of FACT-BP in comparison to the BPI assessment in the context of a pilot randomized prospective trial comparing a de-escalating bisphosphonate regimen (12 week) to the standard 3–4 weekly regimen. BPI is a commonly used instrument for assessment of bone pain and its interference with independent functioning and quality of life in cancer patients in large clinical trials and in routine clinical activity. While it is short and simple to use, it is less specific with respect to its ability to assess the impact of pain on patients’ quality of life. The FACT-BP questionnaire is a relatively brief alternative, though not as brief as BPI, but it covers a wider range of relevant content. This includes more detailed and specific characteristics of cancer-related bone pain, its impact on a patient’s ability to walk, perform regular daily activity, and ability to work. The FACT-BP questionnaire also covers important patient psycho-social aspects such as ability to cope with pain, influence of bone pain on patients’ anxiety level and their overall view of their malignant condition, as well as the influence of their pain on social activity and family life.

The current results show that FACT-BP and BPI correlated well with each other over time. In addition, using either of these methods of assessment of pain, no differences were observed between the pain scores in the two study arms. While interestingly, we acknowledge the limitations of the current study. REFORM was a small randomized pilot study, thus it remains possible that the small number of patients analyzed presently could impact the present results. However, our findings support the use of FACT-BP in larger cohorts assessing bone targeted trials, particularly those focused on patients considered to be at low risk, as levels of the standard bone turnover biomarkers CTx and BSAP may not truly reflect the impact of the disease on a patient’s well being. Our reasoning for this choice is that it correlates quite well with the most commonly-used pain instrument in prior bone pain trials, the BPI, and yet it introduces a wider variety of content which enhances the validity and applicability of the assessment to patients’ lives [2]. We thus plan to incorporate FACT-BP in larger bone-targeted trials for further evaluation of its validity.

It is also of interest that while the biomarker of bone turnover measured in this study, namely CTx, correlated with pain as measured by both assessment tools at baseline, CTx levels did not appear to correlate with pain scores when measured at 12 weeks on study. While the reasons for this remain unclear, we speculate that the modest, but statistically insignificant rise in CTx levels observed in patients in the de-escalated treatment arm may contribute to the lack of correlation with pain scores at 12 weeks. Importantly, however, despite modest rises in CTx, pain scores were not significantly different in the two treatment arms suggesting that de-escalation of bisphosphonate treatment in this low risk group can still effectively control patient’s pain.

In conclusion, the FACT-BP is a validated questionnaire assessing patient reported issues around metastatic bone disease. In order for us to improve the care of our patients we need reliable yet pragmatic scores that can be used to drive practice changing...
research and also standard patient care in the real world, non-trial setting. In addition, we need more studies evaluating the correlation between subjective measures such as pain score and objective biomarker measures so that smaller trials can be designed to answer important clinical questions without the need for SREs to be the primary study endpoint.

Conflict of interest statement

Jennifer Beaumont – consultant in FACIT.org.
There is no conflict of interest for other authors.

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