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Research paper

Effects on bone resorption markers of continuing pamidronate or switching to zoledronic acid in patients with high risk bone metastases from breast cancer

J.F. Hilton[a], M. Clemons[a,b], G. Pond[c], H. Zhao[b], S. Mazzarello[b], L. Vandermeer[b], C.L. Addison[b,*]

[a] Division of Medical Oncology and Department of Medicine, The Ottawa Hospital, University of Ottawa, Ottawa, ON, Canada
[b] Ottawa Hospital Research Institute and University of Ottawa, Department of Medicine, Ottawa, Ontario, Canada
[c] Department of Oncology, McMaster University, Hamilton, ON, Canada

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ABSTRACT

Background: Switching patients who remain at high risk of skeletal related events (SREs) despite pamidronate to the more potent bisphosphonate zoledronate, may be an effective treatment strategy. As part of a previously reported clinic study in this setting, we evaluated whether biomarkers for bone resorption, such as Bone-Specific Alkaline Phosphatase (BSAP), bone sialoprotein (BSP), and N-terminal telopeptide (NTX) correlated with subsequent SRE risk.

Methods: Breast cancer patients who remained at high risk of SREs despite at least 3 months of q.3–4 weekly pamidronate were randomized to either continue on pamidronate or to switch to zoledronate (4 mg) once every 4 weeks for 12-weeks. High risk bone metastases were defined by either: occurrence of a prior SRE, bone pain, radiologic progression of bone metastases and/or serum C-terminal telopeptide (CTx) levels > 400 ng/L despite pamidronate use. Serum samples were collected at baseline and weeks 1, 4, 8 and 12 (CTx and BSAP) and baseline and week 12 (NTx and BSP), and all putative biomarkers were measured by ELISA. Follow up was extended to 2 years post trial entry for risk of subsequent SREs. The Kaplan-Meier method was used to estimate time-to-event outcomes. Generalized estimating equations (GEE) were used to evaluate if laboratory values over time or the change in laboratory values from baseline were associated with having a SRE within the time frame of this study.

Results: From March 2012 to May 2014, 76 patients were screened, with 73 eligible for enrolment. All 73 patients were available for biochemical analysis, with 35 patients receiving pamidronate and 38 patients receiving zoledronate. The GEE analysis found that no laboratory value was associated with having a subsequent SRE. Interaction between visit and laboratory values was also investigated, but no interaction effect was statistically significant. Only increased number of lines of prior hormonal treatment was associated with subsequent SRE risk.

Conclusion: Our analysis failed to find any association between serum BSAP, BSP, CTx or NTx levels and subsequent SRE risk in this cohort of patients. This lack of correlation between serum biomarkers and clinical outcomes could be due to influences of prior bisphosphonate treatment or presence of extra-osseous metastases in a significant proportion of enrolled patients. As such, caution should be used in biomarker interpretation and use to direct decision making regarding SRE risk for high risk patients in this setting.

1. Introduction

Bone-targeted agents, such as bisphosphonates and denosumab, have been standard of care for delaying the onset and reducing the frequency of skeletal-related events (SREs) in patients with bone metastases from a range of malignancies including breast cancer [1–5]. SREs are traditionally defined as; radiotherapy and/or surgery to bone, pathological fractures, spinal cord compression, and hypercalcemia [1–4]. Despite their widespread use, there are still multiple questions regarding the optimal duration, frequency, and ideal bone-targeted agent. As a result, the ASCO guideline on bone-targeted agent used for metastatic breast cancer makes no recommendation with regards to use of pamidronate, zoledronate, or denosumab [6]. Given the direct costs of these agents, as well as the increased toxicity associated with the use

* Correspondence to: Box 926, 501 Smyth Road, Ottawa, ON, Canada K1H 8L6.
E-mail address: caddison@ohri.ca (C.L. Addison).

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of more potent agents [4,7], an alternative strategy would be to use a less potent agent initially in all patients and then switch to a more potent agent in those patients who remain at high risk of further SREs.

Previous studies have evaluated outcomes when switching from one bone-targeted agent to another, usually more potent bone-targeted agent [8,9]. These studies showed that switching resulted in a fall in biomarkers for bone resorption or improvement in pain scores; however, only one study, which was not adequately powered, showed a potential reduction in SRE rates [8–13]. Our group previously reported a 12-week, randomized, double-blind, placebo-controlled trial assessing the efficacy of switching patients with high risk bone metastases already receiving pamidronate to the more potent bisphosphonate, zoledronate (ODYSSEY study) [14]. In the ODYSSEY study, high risk metastatic bone disease was defined as; the occurrence of either; a prior SRE, and/or current bone pain, and/or radiological progression of bone metastases, and/or serum C-terminal telopeptides (CTx) > 400 ng/L, despite pamidronate use. We reported that although switching resulted in a decrease in CTx, there were no significant improvements in bone pain, quality of life or subsequent SREs.

Although previous studies have shown that higher levels of CTX is associated with worse survival and that normalization of high levels of CTX with bisphosphonates is associated with improved pain scores, it is possible that CTX levels may not represent an ideal biomarker for patients already on bone-targeted agents [15,16]. Other biomarkers, such as bone-specific alkaline phosphatase (BSAP), bone sialoprotein (BSP) or serum N-terminal telopeptides (NTX) may represent an improvement on CTX. BSAP is produced by mature osteoblasts and is involved in bone matrix mineralization [17,18]. Circulating levels of BSAP have been shown to correlate with the presence of osseous metastases [19–21] and correlate with outcome for patients on bone targeted agents [16,22–24]. BSP is known to play a role in bone mineralization and can be produced by numerous cell types including tumor cells [25]. BSP has also been shown correlate with bone metastasis and patient survival in breast cancer [26–29]. NTX is a N-terminal fragment of collagen that is generated during tumor-induced degradation of bone collagen, and has been previously used as a surrogate marker of bone turnover, SRE risk and survival [8,9,30]. As part our study, BSAP, BSP, and NTX were evaluated as part of an exploratory biomarker analysis with the results presented here.

2. Methods

2.1. Overview of the Odyssey study design

The Odyssey study (NCT01907880) [14] enrolled patients with metastatic breast cancer and radiologically confirmed bone metastases who had received at least 3 months of q.3–4 weekly intravenous pamidronate therapy for their disease. To participate, patients must have evidence of continued high risk metastatic bone disease defined as either; the occurrence of a prior SRE, bone pain, and/or radiologic progression of bone metastases and/or serum CTX levels > 400 ng/L despite pamidronate use. Patients were not eligible if they had an acute untreated SRE or a change or an anticipated change in systemic therapy within 28 days prior or after entering the study. Eligible patients were randomly assigned using a stratified block design to either continue on pamidronate or to switch to zoledronate (4 mg) once every 4 weeks for 12 weeks. Further details regarding the stratification, blinding, toxicity and quality of life assessments are previously published [14]. The primary end point of the Odyssey study was the proportion of patients experiencing a drop in CTX over the 12-week study between the two arms. The current biochemical analysis represented a secondary end point for the study. The follow up period was extended to 2 years after study entry for the occurrence of subsequent SREs.

2.2. Biochemical analysis

Serum samples were collected after an overnight fast, prior to receiving the study drug and then on weeks 1, 4, 8 and 12 post-treatment. Serum BSAP was measured at each of these time points while serum BSP and urine NTX were only measured at baseline and week 12. Serum samples were allowed to clot, and were then centrifuged for 10 min at 3000 RPM. Both serum and urine samples were frozen at − 80 °C until analysis. Serum CTX was measured by a chemiluminescence immunoassay using CrossLaps® on an IDS iSYS automated analyzer. Serum BSAP was measured by a chemiluminescence immunoassay, Ostase®, on the Beckman Coulter unicel DxI. Urine NTx levels were measured using the Osteomark assay (Alere, Scarborough ME, detection limit 2 nM BCE/mM creatinine), Serum BSP was measured using quantitative human specific ELISA kits (Abexa, Cambridge UK, detection limit ~ 60 ng/ml).

2.3. Statistical analysis

Descriptive statistics were used to summarize baseline characteristics, laboratory values and outcomes. The Kaplan-Meier method was used to estimate time-to-event outcomes. Cox regression analysis was used to investigate baseline factors potentially prognostic for time to first SRE. These models were stratified for treatment arm and stratification factors. Generalized estimating equations (GEE) were used to evaluate if lab values over time (baseline, 1, 4, 8, and 12 weeks), or the change in lab values from baseline (at weeks 1, 4, 8 and 12) were associated with having a SRE within the time frame of this study. Statistical significance was defined as a p-value of 0.05 or less.

3. Results

From March 2012 to May 2014, 76 patients were screened, with 73 eligible for enrolment. As the rate of accrual slowed markedly with results of the de-escalated bisphosphonate trials [29,31,32] the study was closed on the recommendation of the study Data Safety Monitoring Committee before reaching its planned sample size of 93 patients. Serum from all 73 enrolled patients was available for biochemical analysis, with 35 patients receiving pamidronate and 38 patients receiving zoledronate. Descriptive baseline characteristics for the participants are shown in Table 1. The study arms were well balanced in terms of patient age, duration of bone metastases, prior lines of systemic therapy and occurrence of SREs before randomization.

The results of the biochemical analyses over time are shown in Table 2. Baseline levels for all four measured biomarkers were similar in both groups. In terms of CTX levels, patients on pamidronate and zoledronic acid show similar modest decreases in sCTX levels 1 week post treatment initiation. However, while levels continued to decline in both groups over the remaining study period, the median change in sCTX was much larger in those patients receiving zoledronic acid as compared to pamidronate (decreases of 100 vs 25 ng/L). Similarly, urinary NTX levels declined more substantially, by approximately 2.5-fold, in patients receiving zoledronate than in those that continued on pamidronate. Nevertheless, this observation was not consistent when compared to the other markers of bone turnover. In terms of BSAP levels, patients receiving pamidronate and zoledronate qualitatively experienced similar and modest declines in marker level. In terms of BSP levels, patients receiving pamidronate demonstrated a slight and likely insignificant decline in median BSP levels whereas patients receiving zoledronate essentially showed no difference in median levels at 12 weeks post treatment as compared to levels at baseline.

In this study, we also correlated baseline biomarkers or changes of biomarkers over time with time to first SRE. Of the evaluable patients, 23/73 (31.5%) had an SRE within the 2 year time frame of the study follow-up. Of these, 13 (56.5%) were in the zoledronic acid arm, and 10 (43.5%) were in the pamidronate arm. The majority of first SRE were

Table 1
Baseline patient characteristics.

		All patients	Pamidronate	Zoledronate
N		73	35	38
Strata	SRE, pain	43 (58.9)	21 (60.0)	22 (57.9)
	SRE, no pain	7 (9.6)	4 (11.4)	3 (7.9)
	No SRE, pain	15 (20.6)	7 (20.0)	8 (21.1)
	No SRE, no pain	8 (11.0)	3 (8.6)	5 (13.2)
Baseline SRE	N (%) Yes	50 (68.5)	25 (71.4)	25 (65.8)
Baseline pain	N (%) Yes	58 (79.5)	28 (80.0)	30 (79.0)
Age	Mean (std dev)	60.6 (11.3)	58.7 (12.1)	62.3 (10.4)
BMI	Mean (std dev)	27.3 (4.7)	27.0 (5.2)	27.6 (4.3)
Duration of bone mets, months	Median (range)	11 (1, 120)	9 (1, 120)	12.5 (3, 62)
Sites of metastases[a]	Brain	5 (6.9)	4 (11.4)	1 (2.6)
	Lung	19 (26.0)	9 (25.7)	10 (26.3)
	Liver	27 (37.0)	15 (42.9)	12 (31.6)
	Soft Tissue	4 (5.5)	2 (5.7)	2 (5.3)
	Other	28 (38.4)	11 (31.4)	17 (44.7)
	None (Bone)	19 (26.0)	10 (28.6)	9 (23.7)
Time from breast cancer to development of metastases, Months	Median (range)	20 (0, 300)	34 (0, 300)	10 (0, 276)
Prior lines of chemotherapy for metastatic disease	0	27 (37.0)	16 (45.7)	11 (29.0)
	1	20 (27.4)	5 (14.3)	15 (39.5)
	2	18 (24.7)	9 (25.7)	9 (23.7)
	3+	8 (11.0)	5 (14.3)	3 (7.9)
Prior lines of endocrine therapy for metastatic disease	0	10 (13.7)	4 (11.4)	6 (15.8)
	1	43 (58.9)	20 (57.1)	23 (60.5)
	2	17 (23.3)	9 (25.7)	8 (21.1)
	3+	3 (4.1)	2 (5.7)	1 (2.6)
Total prior lines of bone chemotherapy + Hormone Therapy	1	26 (35.6)	10 (28.6)	16 (42.1)
	2	14 (19.2)	9 (25.7)	5 (13.2)
	3+	33 (45.2)	16 (45.7)	17 (44.7)
Duration of Bisphosphonate, months	Median (range)	10 (3, 118)	10 (3, 118)	11 (3, 60)
Prior radiation for bone pain	0	48 (65.8)	24 (68.6)	24 (63.2)
	1	20 (27.4)	9 (25.7)	11 (29.0)
	2	4 (5.5)	1 (2.9)	3 (7.9)
	3	1 (1.4)	1 (2.9)	0 (0.0)
Prior preventative radiotherapy	0	61 (83.6)	30 (85.7)	31 (81.6)
	1	11 (15.1)	4 (11.4)	7 (18.4)
	2	1 (1.4)	1 (2.9)	0 (0.0)
Prior bone surgery	N (%) Yes	3 (4.1)	1 (2.9)	2 (5.3)
Prior Hypercalcemia	N (%) Yes	2 (2.7)	1 (2.9)	1 (2.6)
Prior Spinal Cord Compression	N (%) Yes	4 (5.5)	1 (2.9)	3 (7.9)
Prior Pathologic Fracture	N (%) Yes	11 (15.1)	6 (17.1)	5 (13.2)
Prior SRE Total	0	41 (56.2)	20 (57.1)	21 (55.3)
	1	17 (23.3)	9 (25.7)	8 (21.1)
	2	7 (9.6)	2 (5.7)	5 (13.2)
	3	3 (4.1)	1 (2.9)	2 (5.3)
	4	1 (1.4)	1 (2.9)	0 (0.0)
	5	4 (5.5)	2 (5.7)	2 (5.3)

SRE = skeletal related event.
[a] May have had multiple sites of metastases.

radiotherapy for pain (19/23, 83%), with 11 of these patients being on the zoledronic acid arm, and 8 on the pamidronate arm. The next most frequent first SRE was pathological fracture (4/23, 17%), with 2 patients being in each treatment arm. Table 3 shows the univariable results looking at baseline factors potentially prognostic for time to first SRE after study entry. The number of lines of prior hormonal therapy received was the only statistically significant (p = 0.036) factor at baseline associated with time to first SRE. Those patients with an increased number of lines of prior hormonal therapy were at an increased risk of having an SRE (hazard ratio = 1.77, 95% CI = 1.04 to 3.01). Having a prior SRE trended towards an increased risk for having a future SRE, but this did not reach statistical significance (hazard ratio = 2.43, 95% CI = 0.832 7.17, p = 0.11). Baseline pain also trended towards statistical significance in terms of SRE risk (hazard ratio = 6.87, 95% CI = 0.93–51.00, p = 0.059). No biochemical markers for bone turnover when measured at baseline were statistically significant for predicting future SRE risk.

As baseline levels of markers were not correlated with risk of SRE events, we used Generalized Estimating Equations analysis to assess the association of lab values across time with a future SRE. Results are presented in Table 4. No laboratory value for any biochemical marker for bone turnover was shown to be associated or prognostic for having an on study SRE when either raw values or percentage change from baseline values were used. Fig. 1 illustrates the percentage changes for each of sCTX (Fig. 1A), BSAP (Fig. 1B), uNTX (Fig. 1C) and BSP (Fig. 1D). Although statistical significance was not reached for any of these markers, it is interesting to note the separation of the curves for biomarker changes over time observed for BSAP, uNTX and BSP in this study. Due to small sample sizes and low number of event rates, we are unable to evaluate whether this is occurring in all patients who experience SRE regardless of bisphosphonate treatment or is being driven by the type of bisphosphonate used. Unlike other studies which suggest that patients who do not experience > 40% drops in NTX levels at 3 months post treatment initiation are more likely to experience SRE, we found that only 38.5% of patients who experienced SRE did not have decreases in NTX, while 61.5% of patients who experienced a SRE did have > 40% drops in NTX levels.

Table 2
Week 12 clinical and biomarker values.

		All patients	Pamidronate	Zoledronate
N		73	35	38
Median (range) CTx (ng/L)	Baseline	200 (18.6, 2370)	200 (18.6, 1680)	190 (30, 2370)
	Week 1	80 (30, 870)	113 (30, 870)	60 (30, 490)
	Week 4	138 (30, 3000)	210 (30, 1420)	82.5 (30, 3000)
	Week 8	120 (30, 1500)	180.5 (30, 1500)	80 (30, 630)
	Week 12	110 (30, 1810)	195.5 (30, 1810)	89.5 (30, 500)
Median (range), Change in CTx (ng/L)	Week 1	− 100 (− 2030, 670)	− 90 (− 1110, 670)	− 100 (− 2030, 0)
	Week 4	− 69.5 (− 1600, 2960)	− 30 (− 620, 730)	− 110 (− 1600, 2960)
	Week 8	− 70 (− 1740, 780)	− 30 (− 1170, 780)	− 90 (− 1740, 10)
	Week 12	− 60 (− 1870, 580)	− 25 (− 860, 580)	− 100 (− 1870, 80)
Median (range) BSAP (IU/L)	Baseline	11 (3.4, 90)	10.5 (3.4, 90)	11 (5.9, 65.1)
	Week 1	10.1 (2.2, 38.3)	9.8 (2.2, 38.3)	10.2 (2.2, 34.6)
	Week 4	10.6 (4.4, 43.7)	10.5 (4.7, 38.3)	10.6 (4.4, 43.7)
	Week 8	10.8 (4.7, 35.1)	11.0 (4.8, 27.0)	10.4 (4.7, 35.1)
	Week 12	10.0 (4.5, 27)	10.5 (4.5, 27.0)	9.0 (5.1, 25.4)
Median (range), Change in BSAP (IU/L)	Week 1	− 0.1 (− 57.8, 8.9)	− 0.1 (− 57.8, 8.9)	0 (− 31.4, 5.5)
	Week 4	− 0.6 (− 77.3, 6.3)	− 0.3 (− 77.3, 6.3)	− 1.0 (− 38.2, 3.1)
	Week 8	− 0.9 (− 57.5, 10.8)	− 0.3 (− 57.5, 10.8)	− 1.0 (− 49.6, 3.1)
	Week 12	− 1.3 (− 81.3, 4.1)	− 0.8 (− 81.3, 4.1)	− 1.6 (− 53.3, 2.3)
Median (range) NTx (nM BCE/mM creatine)	Baseline	241.2 (8.9, 2257.1)	263.7 (34.8, 2257.1)	194.2 (8.9, 1924.8)
	Week 12	123.7 (5.4, 1830.6)	133.7 (5.4, 1627.6)	108.9 (15.6,1830.6)
Change in NTx to week 12 (nM BCE/mM creatine)	Median (range)	− 54.0 (− 1068, 657)	− 41.3 (− 1068, 657)	− 101.5 (− 856, 155)
Median (range) BSP (ng/ml)	Baseline	23.4 (5.3, 84.6)	23.6 (7.8, 75.5)	23.2 (5.3, 84.6)
	Week 12	22.4 (2.7, 84.8)	21.5 (6.5,84.8)	25.7 (2.7, 65.2)
Change in BSP to week 12 (ng/ml)	Median (range)	− 1.2 (− 47.4, 64.0)	− 3.1 (− 26.9, 64.0)	1.3 (− 47.4, 34.2)
Progression-free survival	N (%) Events	15 (20.5)	8 (22.9)	7 (18.4)
	Median (95% CI)	Not Reached	Not Reached	Not Reached
	60-day (95% CI)	83.6 (72.9, 90.3)	82.9 (65.8, 91.9)	84.2 (68.2, 92.6)
	120-day (95% CI)	79.5 (68.3, 87.1)	77.1 (59.5, 87.9)	81.6 (65.2, 90.8)
SRE	N (%) Yes	23 (31.5)	10 (28.6)	13 (34.2)
SRE type	Path Fracture	4 (17.4)	2 (20.0)	2 (15.4)
	Rx for bone pain	19 (82.6)	8 (80.0)	11 (84.6)
SRE-free survival	N (%) Events	23 (31.5)	10 (28.6)	13 (34.2)
	Median (95% CI)	Not Reached	Not Reached	Not Reached
	90-day (95% CI)	93.2 (84.3, 97.1)	94.3 (79.0, 98.5)	92.1 (77.5, 97.4)
	1-year (95% CI)	82.2 (71.3, 89.2)	74.3 (56.4, 85.7)	89.5 (74.3, 95.9)
	2-year (95% CI)	68.5 (56.5, 77.8)	71.4 (53.4, 83.5)	65.8 (48.5, 78.5)
Study status	Completed Study	64 (87.7)	31 (88.6)	33 (86.8)
	PD	3 (4.1)	2 (5.7)	1 (2.6)
	Patient Choice	3 (4.1)	0 (0.0)	3 (7.9)
	MD Choice	3 (4.1)	2 (5.7)	1 (2.6)
Overall survival	N (%) Events	12 (16.4)	4 (11.4)	8 (21.0)
	Median (95% CI)	Not Reached	Not Reached	Not Reached
	180-day (95% CI)	93.2 (84.3, 97.1)	97.1 (81.4, 99.6)	89.5 (74.3, 95.9)
	1-year (95% CI)	89.0 (79.3, 94.4)	94.3 (79.0, 98.5)	84.2 (68.2, 92.6)
	2-year (95% CI)	83.6 (72.9, 90.3)	88.6 (72.4, 95.6)	78.9 (62.3, 88.9)

Table 3
Prognostic factors at baseline for time to first SRE.

	Type	N	Hazards ratio (95% CI)	P-value
Univariable analyses				
Treatment arm[a]	Pamidronate vs ZA	73	0.89 (0.39, 2.03)	0.77
Baseline SRE[b]	Yes vs No	73	2.43 (0.83, 7.17)	0.11
Baseline pain[b]	Yes vs No	73	6.87 (0.93, 51.00)	0.059
Prior Chemotherapy for Metastatic Disease, # of Lines	Continuous	73	0.89 (0.67, 1.19)	0.44
Prior Hormonal Therapy for Metastatic Disease, # of Lines	Continuous	73	1.77 (1.04, 3.01)	0.036
Prior Lines of Therapy for Metastatic Disease	Continuous	73	1.02 (0.79, 1.32)	0.88
Lung Metastases	Yes vs No	73	0.73 (0.27, 1.99)	0.54
Liver Metastases	Yes vs No	73	0.64 (0.26, 1.57)	0.33
Metastases	None vs At least one	73	1.68 (0.64, 4.40)	0.29
Number of SRE	Continuous	73	1.15 (0.87, 1.51)	0.32
Age	Continuous	73	1.00 (0.96, 1.04)	0.94
BMI	Continuous	73	1.05 (0.95, 1.15)	0.34
CTx (ng/L)	Logarithmic	73	1.19 (0.75, 1.87)	0.46
BSAP (IU/L)	Logarithmic	73	1.46 (0.79, 2.71)	0.22
NTx (nM BCE/mM creatine)	Logarithmic	67	1.07 (0.73, 1.56)	0.75
BSP (ng/ml)	Logarithmic	73	0.81 (0.31, 2.16)	0.68

All others are adjusted for treatment arm and stratification factors.
[a] Adjusted for stratification factors.
[b] Adjusted for treatment arm.

Table 4
Association of lab values across time points with SRE, Generalized Estimating Equations. Is variable prognostic over time for SRE.

Variable	Type	Estimate (95% CI)	P-value
Raw Data, Adjusted for Visit			
CTx (ng/L)	Logarithmic	0.22 (− 0.62, 0.23)	0.36
BSAP (IU/L)	Logarithmic	− 0.56 (− 1.41, 0.30)	0.20
NTx (nM BCE/mM creatine)	Logarithmic	− 0.09 (− 0.54, 0.36)	0.69
BSP (ng/ml)	Logarithmic	− 0.18 (− 1.11, 0.74)	0.70
Change From Baseline, Visit 2 On, Adjusted for Visit			
CTx (ng/L)	change	0.0003 (− 0.0012, 0.0018)	0.72
BSAP (IU/L)	change	0.0196 (− 0.0360, 0.0408)	0.90
NTx[a] (nM BCE/mM creatine)	change	− 0.0006 (− 0.0036,0.0024)	0.69
BSP[a] (ng/ml)	change	0.0163 (− 0.0187, 0.0513)	0.36

[a] Change to week 12 only value.

4. Discussion

The Odyssey study was the only randomized, double-blind, placebo-controlled trial assessing the efficacy of switching patients with high risk bone metastases already receiving pamidronate to the more potent bisphosphonate, zoledronate [14]. The study failed to demonstrate any improvement in measures of bone pain or quality of life when switching from a less potent bisphosphonate to a more potent one despite significantly more reduction in serum CTx levels in the zoledronate arm. In addition, patients receiving zoledronate had similar rates and types of SREs during the 12 weeks of the study compared to those receiving pamidronate. Finally, use of the more potent bisphosphonate was associated with greater toxicity.

In an era where there are increased attempts at fiscal control and personalised medicine, a number of strategies are being explored to optimise the use of bone-targeted therapies. These include de-escalation strategies for pamidronate, zoledronate and denosumab [33]. In addition, given that current international treatment guidelines make no preferential choice for which of these 3 agents to use in patients with bone metastases from breast cancer [6] then an alternative may be to use a cheaper, less toxic agent for all patients and then switch to a more potent agent in those patients who have the highest risk of subsequent SREs. A previous open label study by Body et al. [34] showed a significant decrease in bone-resorption markers with denosumab following intravenous bisphosphonate, but did not report a significant decrease in SRE rates. Similar findings were seen in single-arm studies of a switch from pamidronate to zoledronate and ibandronate [8,9]. The Odyssey study was the first to evaluate a switch from pamidronate to

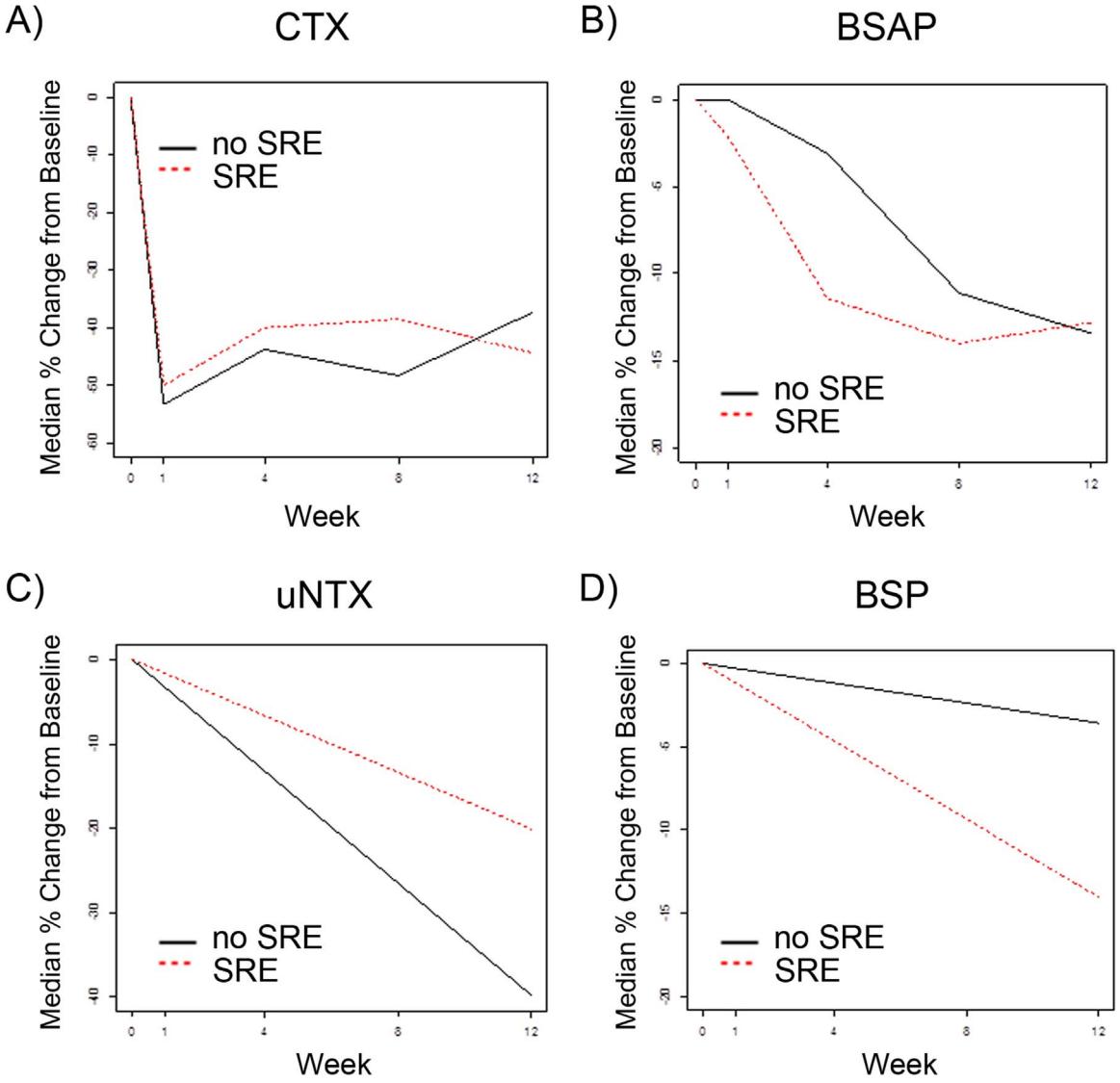

Fig. 1. Changes in biomarker over time as correlated with SRE outcome. A) sCTX; B) BSAP; C) uNTX; D) BSP.

zoledronate in a double-blind manner. While showing that a switch to zoledronate was associated with a reduction in CTX, this was not associated with any significant difference in pain, or SREs during the 12 weeks of study. Nevertheless, the routine collection of serum has enabled us to evaluate whether other markers of bone turnover could be used to identify those patients at further subsequent risk of SREs over a longer follow up period and for whom switching to a more potent agent may reduce this risk.

Changes in biomarkers of bone turnover are often used in clinical trials evaluating bone-targeted agents; however, it is recognized in the literature that they are at best a poor surrogate marker for subsequent SRE risk. The most commonly used biomarker is serum CTX, which when elevated, has been shown in some previous studies to be associated with worse survival [24]. However, these studies used changes from baseline levels CTX (i.e. measured prior to commencement of bone-targeted therapy), unlike in our study where we were evaluating changes in patients already established on therapy. Similar to our current findings, we have also previously observed no changes in CTX levels from baseline to on-study when patients were switched from a 3–4 weekly pamidonate treatment to a de-escalated treatment regimen of every 12 weeks [29]. With the lack of correlation of CTX levels over time with clinical parameters of interest, we explored whether serum BSAP, BSP, and NTX have potential as surrogates for subsequent SRE risk.

Our study attempted to limit factors that may contribute to biomarker change in order to facilitate a robust analysis, such as controlling for diurnal effects and preventing changes in systemic therapy within a month before and after randomization. Unfortunately, our analysis failed to find any association between baseline serum CTX, BSAP, BSP, or urine NTX levels and subsequent SRE risk. This is consistent with our previous observations regarding the inability of CTX levels to predict SRE [35]. Although many of these markers have been shown to be associated with survival, and are likely indicative of increased disease burden, they do not seem to correlate with risk of SRE. Our findings are not in line with those of others who have shown baseline NTX correlates with SRE risk [15,36–38]. It is important to note a few differences between these studies and ours with respect to the patient populations. For the majority of these studies, patients were bisphosphonate naïve, or had a low percentage (~ 23% [15]) of patients who had received prior bisphosphonate treatment, unlike in our study where 100% of patients had received prior bisphosphonate treatment and continued on treatment immediately prior to randomization. Additionally, these other studies accrued patients with all levels of bone metastatic disease, whereas the present study only enrolled patients considered to be high risk bone metastatic patients (ie CTX levels > 400 ng/L at study entry). Our study is in line with that of Brown et al. [38], who also showed that in a large Phase III study of bone metastatic patients treated with zoledronic acid that CTX and NTX levels did not correlate with SRE, although unlike our study they did demonstrate an association with BSAP and SRE risk. However, also in support of our findings it has been shown that in patients who experience SREs less than 10% of them show changes in NTX [39], and as such it was not predictive of impending SRE. Barnadas et al. also showed that NTX and BSAP failed to correlate with SRE in breast cancer patients treated with zoledronic acid [22]. Interestingly it has recently been published that bone metastatic patients who additionally have extraskeletal metastases have very erratic changes in their levels of uNTX [40]. As the majority of patients in our study also had extraskeletal metastases in addition to bone metastases (~ 75%) this could also be a significant confounding factor to our study and explain in part the lack of correlation with important bone metastases phenotypes such as SRE.

Although not statistically significant, it is interesting to note that the magnitude of change of uNTX and BSP from baseline to 12 weeks did show a separation of the curves with those patients experiencing SRE having smaller and larger decreases for uNTX and BSP respectively. Biologically this is in line with worse overall bone turnover given that NTX is a cleavage product generated by bone degradation and BSP is usually involved in bone mineralization, so smaller drops in NTX would be associated with continued degradation, while larger drops in BSP would be consistent with failure to promote bone formation. These differential changes over time are reminiscent of measures of rates of change or velocity, and indeed it has recently been shown that BSAP velocity is associated with worse overall survival in prostate cancer patients [23,41], however its association with SRE were not evaluated in these studies. It would be interesting to evaluate these two markers in particular in extended time courses of analysis, and perhaps develop a composite score of their velocities over time to determine if an association with SRE exists.

Currently, there is limited data guiding physicians with regards to the ideal treatment for patients who develop an SRE while on bone-resorption agents [9,11]. Although current evidence suggests that these patients should continue on a bone-resorption agent, as this does increase the time to the development of subsequent SREs, it is uncertain whether or not switching to a different agent such as denosumab or a more potent agent such as zoledronate is helpful given that similar SRE rates were observed in the 2 arms of this study [7,42]. Unfortunately our present study does not support the use of these biomarkers as predictors of SRE risk, and when compared to other studies, suggests that factors such as prior bisphosphonate use and presence of extra-osseous metastases could be significant confounders to the interpretation of the meaning of their levels in patients treated outside the clinical trial setting.

We acknowledge there are limitations to this analysis. The original Odyssey study did not reach its planned sample size and the study was closed prematurely due to many physicians and patients opting for de-escalated 12-weekly therapy [14]. It is possible that a relationship would have been observed had the study met its pre-planned sample size. Our study is also limited by the number of SRE events, which was a total of 23. Although previous studies evaluating CTX levels showed that falling levels correlate with symptomatic response to pamidronate and that baseline CTX levels can predict for SREs during the first 3 months of therapy [43], it is possible that 3 months of therapy may not be long enough to reflect outcomes with regards to serum biomarker levels. Previous studies of pamidronate and zoledronate in breast cancer patients did not show significant differences in rates of SREs until 25 months follow-up in a bisphosphonate naïve population and it is possible that a longer period of assessment is necessary to demonstrate biomarker utility [7,44]. However, it is also possible that the presence of extraskeletal metastases confounds the biomarker readouts, and suggests studies powered to investigate bone turnover markers in bone metastasis only patients could show useful associations with biomarkers of bone turnover and SRE risk. The current study did however have advantages over other studies in that the protocols for serum collected were rigorously adhered to with all specimens being first-pass morning collections as this known to reduce variability in turnover markers levels. The study was also double-blinded and this may explain why the improvements in QoL scores observed in the original open label study where all patients were switched from pamidronate to zoledronate, were not seen in the Odyssey study [9,10].

In conclusion, it does not appear that either baseline levels or changes in levels over time of a biomarker panel for bone resorption correlates with clinical outcomes such as SRE in high risk bone metastasis patients receiving bone-resorption agents. At the current time, these biomarkers are not utilized routinely and this study does not support their use as predictors of SRE risk. However, our findings suggest that other studies in larger cohorts should pay attention to the effects of factors such as prior and concurrent bisphosphonate use at study entry, and to the presence and extent of extra-osseous metastasis in the respective patient populations to confirm whether these and other parameters may influence biomarker levels and compromise their use as predictors of SRE or outcome.

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