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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

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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

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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