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ORIGINAL ARTICLE

Procollagen type I N-propeptide is a predictor of skeletal morbidity in patients with malignant osteolytic bone disease on bisphosphonates

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Abstract
Background There is an urgent need for individualized treatment of malignant bone disease (MBD), as the clinical benefit from bone-targeted therapies is moderate. We assessed the predictive value of the bone formation marker procollagen type I N-propeptide (PINP) for skeletal morbidity in patients with MBD receiving pamidronate.
Methods Seventy patients with advanced MBD were randomized to receive pamidronate 60 mg ($n = 35$) or 90 mg ($n = 35$) every 3 weeks for six cycles in a double-blind study. PINP was analyzed at baseline and before each administration of pamidronate, using a validated ELISA. Serum PINP concentrations were compared with pain response (visual analog scale VAS, composite pain score) and skeletal morbidity (skeletal-related events, SRE) using Student's *T*-test, Wilcoxon rank-sum and log-rank test, respectively.
Results Patients with ≥20% pain reduction in the VAS had lower baseline PINP concentrations when compared to patients with <20% VAS response ($P < 0.0001$). A high baseline serum PINP concentration (highest tertile versus lower two tertiles) was significantly associated with a shorter duration of pain response ($P < 0.0001$) and a shorter time interval to first SRE ($P < 0.008$). Sensitivity of a low baseline PINP serum concentration for freedom from SRE at 1 year from randomization was 75% (15 out of 20 patients), while specificity was 82% (27 out of 33 patients).
Conclusions Serum PINP has been shown to be a significant predictor for skeletal morbidity in patients with MBD on pamidronate treatment. Prospective validation of PINP in patients with MBD to assess the prognosis or individualize bone-targeted treatment is justified.

Keywords N-telopeptide · Malignant bone disease · Pamidronate · Cancer pain · Bone turnover marker

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Introduction

Bone is the most frequent, typically the first, and often the only site of metastasis in patients with advanced solid tumors [1]. The incidence of bone metastases depends on the primary tumor, but is particularly high in patients with advanced breast or prostate cancer, developing in up to 80% of these patients [2]. Type I collagen is formed by three polypeptide chains and comprises up to 90% of total protein in bone. It is synthesized as the large, soluble precursor molecule procollagen I by the osteoblasts [3]. Procollagen type I is converted into collagen type I by the action of procollageneses, which cleave the N- and C-terminal propeptides, followed by spontaneous alignment of the collagen monomers to form microfibrils and finally collagen fibrils [3]. Collagen is again broken down into small peptides by the action of lysosomal enzymes produced by osteoclasts. There are three types of bone metastasis (osteolytic, osteosclerotic and mixed), each reflecting the tumor effects on bone physiology. In osteolytic metastases, bone

resorption is increased but fails to stimulate bone formation adequately [3].

Skeletal morbidity from malignant bone disease (MBD) includes severe pain, hypercalcemia, pathologic fracture, and spinal cord or nerve compression. Skeletal pain is the most common cause of cancer-related pain and is severe and debilitating in two-thirds of patients [2]. Treatment of MBD has been substantially improved by the use of bisphosphonates, and treatment effects include improved pain score, increased bone mineral density and a reduction in secondary skeletal events [4, 5]. As new treatment options such as denosumab [6] enter the clinical stage, it will be of special interest to individualize bone-targeted treatment in these patients. Although several markers provide information on the current status of bone metabolism [7–10], there are no clinical data validating these markers for individualized treatment in patients with MBD. Recently, procollagen type I N-propeptide (PINP) has been validated for analysis in human serum [11]. While NTX is a marker of bone resorption, PINP is a marker of bone formation and has not been studied in patients with MBD and associated bone pain so far. In this study, serum PINP was analyzed in a prospective series of patients with MBD receiving bisphosphonate treatment. The reasons to study PINP were first promising reports on PINP to characterize bone metabolism [12] and tumor spreading to the bone [13] in patients with invasive breast cancer, and detect bone metastases in patients with prostate cancer [14]. The aim of the present study was to assess the predictive value of PINP for pain response and skeletal-related events (SRE) in patients with osteolytic MBD, with the hypothesis that PINP serum concentrations might serve as a surrogate marker for antiresorptive treatment response.

Materials and Methods

Patients and study treatment

Between October 1993 and April 1996, 70 patients with advanced MBD were randomized to receive iv. pamidronate 60 mg ($n = 35$) or 90 mg ($n = 35$) for six 3-weekly cycles in a double-blind, single-institution, prospective study. Eligibility criteria were proven malignancy, malignant osteolytic bone disease by radiological imaging, WHO pain score ≥2, modified WHO analgesic score ≥2, serum creatinine <350 µmol/l and written informed consent. Prior bisphosphonate treatment was permitted, but had to be finished at least 2 months before enrolment. Radiotherapy for intractable bone pain was allowed, provided it was given to <25% of bone lesions. Radiotherapy to a single painful indicator lesion was not permitted. Concomitant systemic antineoplastic treatment was permitted and documented. The protocol has been approved by the ethics committee, and written informed consent was obtained from all patients. Data on pain score [15], bone resorption markers [10] and pharmacoeconomics [16] have been published previously. All patients have deceased, with the cause of death being directly related to the underlying cancer in 65 patients, concomitant cardiac disease in two patients and intercurrent pneumonia in a single patient. Pain assessment was repeated every 3 weeks. Serum concentrations of PINP, bone alkaline phosphatase and standard hematology and biochemistry were taken at baseline and every 3 weeks before administration of pamidronate. Skeletal-related events (SRE), defined as either pathologic bone fracture (vertebral and nonvertebral), spinal cord compression, surgery to bone or radiation to bone [including radioisotopes]) were assessed for each patient. Before each infusion and 3 weeks after the last infusion, treating oncologists recorded each ECOG performance status (PS), WHO pain score (grade 0 = no pain, grade 1 = mild, grade 2 = moderate, grade 3 = severe, grade 4 = intractable pain) and analgesic medication (0 = no analgesics, 1 = mild analgesics (e.g. paracetamol), 2 = nonsteroidal anti-inflammatory drugs, 3 = opiods (e.g. tramadol, codein), 4 = opiates) [15].

Analysis of procollagen type I N-propeptide

Serum samples were stored at −70°C until analysis. Total PINP concentrations were measured on fasting serum at baseline and every 3 weeks before administration of pamidronate, using the Elecsys 2010 automated analyzer (Roche Diagnostics, Basel, Switzerland) as described previously [11]. Diagnostic kits were kindly provided by Roche Diagnostics, Basel. The assay detects both intact mono- and trimetric forms of PINP [17]. More specifically, a biotinylated antibody is incubated with 20 µl of serum, and a second ruthenium-labeled antibody is added together with streptavidin-coated microparticles. These microparticles are magnetically captured onto the surface of an electrode, inducing chemiluminescence emission detected by a photomultiplier. Light emission is quantified and compared to a calibration curve, which is generated by a 3-point calibration. The within-run and between-run (total) imprecision (CVs) were ≤2.3% and ≤5.3%, respectively. The lower limit of quantification (LLQ) was 5 µg/l, and the reference range or cut-off value 95 µg/l.

Statistical analysis

Clinical endpoints were pain response, pain response duration and time to first SRE. Changes of performance status, pain scores and analgesics were classified as improvement or deterioration if the value increased or decreased by one

level on at least two consecutive visits or by ≥2 categories. WHO pain score, analgesic medication and PS were added together and expressed as a percentage of the total maximum score (PPA score) [18]. Pain response was defined as ≥20% reduction in pain intensity on the VAS (VAS response) or in PPA score (PPA response) from baseline on at least two consecutive visits [15, 18]. By doing so, PPA score could be used to control for any effect of systemic treatment or analgesic medication on pain response. Duration of pain response was defined as the time period between the onset of pain response until pain intensity exceeding baseline level or until discontinuation of the study treatment. The study has a power of 80% to detect a 20% difference in pain intensity measured after three infusions ($\alpha = 0.05$, standard deviation 15 mm on the VAS) [18]. Changes of VAS from baseline were analyzed by the Wilcoxon rank-sum test. PINP serum concentrations at baseline, changes of PINP concentrations after 12 weeks (corresponding to four treatment cycles) (in %) and maximum PINP-changes over the entire study treatment (in %) were compared with pain response using Spearman correlation analysis. Additionally, PINP serum concentrations were prospectively categorized into tertiles and compared with pain response using χ^2-test. Duration of pain response and time from randomisation to first SRE were calculated according to the Kaplan–Meier product limit method, and the difference between patients with low or high baseline PINP concentrations was analyzed using the log-rank test. Multivariate logistic regression analysis was performed to test the independent predictive value of baseline PINP concentrations on pain response (by VAS and PPA score), including the following covariates: Patient gender, age, performance score, diagnosis, treatment group (pamidronate 60 or 90 mg infusions), concomitant treatment (chemotherapy, endocrine treatment) and baseline bone alkaline phosphatase. All tests of significance are two-sided; $P < 0.05$ is considered to be significant. All statistical analyses were performed using STATA 10.1 software (STATA Corp, College Station, Texas, U.S.).

Results

Seventy patients were enroled into the study, and 35 patients were randomized to each treatment group. Patient characteristics have been described previously [15]. Seventy-one percent of the patients in the 60 mg group and 77% of the patients in the 90 mg group received the full course of six pamidronate infusions, with a mean of 5.2 pamidronate infusions in both groups (range one to six infusions). The main reason for premature discontinuation of pamidronate was disease progression. More details of treatment adherence and tolerability have been published previously [15]. Mean baseline PINP was 229 µg/l (range 19–1033 µg/l). PINP serum concentrations are outlined according to treatment groups and selected patient characteristics in Table 1. Baseline PINP concentrations were not significantly different between categories of pamidronate dose, malignant disease, age, gender or performance score, but there was a significant difference for concomitant treatment (Table 1). The distribution of breast cancer, myeloma and "other tumors" was not significantly different between the treatment groups. Median percentage change between baseline serum PINP concentrations and

Table 1 Procollagen type I N-propeptide (PINP) serum concentrations according to treatment groups and selected patient characteristics

Covariate	*N* (%)	Mean baseline PINP serum concentration in µg/l (95%-CI)	*P*-value (Student's *T*)
Treatment group			
Pamidronate 60 mg	35 (50)	209 (154–264)	
Pamidronate 90 mg	35 (50)	248 (170–326)	0.21
Patient gender			
Male	14 (20)	249 (119–380)	
Female	56 (80)	223 (172–274)	0.32
Patient age			
>60 years	36 (51)	221 (163–280)	
≤60 years	34 (49)	237 (159–315)	0.37
Baseline ECOG performance status			
0–1	32 (46)	196 (140–251)	
2–4	38 (54)	259 (184–335)	0.09
Diagnosis			
Breast cancer	41 (59)	252 (187–317)	
Multiple myeloma	16 (23)	148 (54–242)	
Other tumors	13 (18)	261 (155–368)	0.16¶
Concomitant antineoplastic therapy			
Chemotherapy	49 (70)	254 (192–317)	
Hormonal treatment	5 (7)	214 (96–332)	
No antineoplastic therapy	16 (23)	146 (89–203)	0.004
Best treatment response			
PR or SD	29 (41)	202 (131–273)	
Progressive disease	41 (59)	249 (185–314)	0.16
Pain response by VAS at week 12			
≥20%	34 (50)	146 (111–181)	
<20%	34 (50)	323 (242–404)	<0.0001
Pain response by PPA score at week 12			
≥20%	17 (29)	169 (79–259)	
<20%	41 (71)	598 (161–289)	0.16

PR partial response, *SD* stable disease, *CI* confidence interval

¶ analysis-of-variance

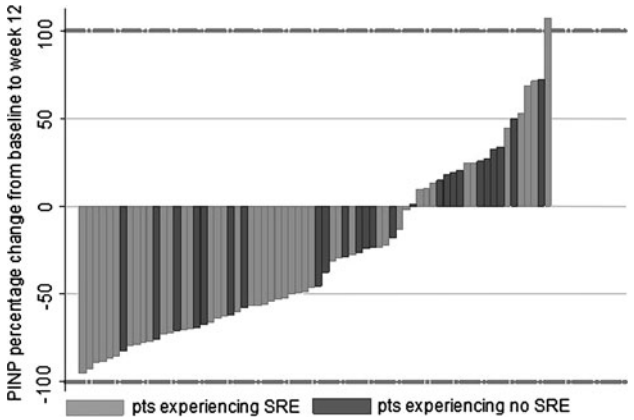

Fig. 1 *Waterfall plot* of the percentage change of serum PINP concentrations between baseline and week 12 (i.e. after four pamidronate treatment cycles); bars are separately marked for patients experiencing a skeletal-related event (SRE) and those not experiencing a SRE at any time

PINP concentration at week 12 was −50% (95%-CI −61% to −28%, $P = 0.02$,), while median maximum percentage change of PINP concentration was −59% (95%-CI −70% to −41%, $P = 0.01$). Mean PINP percentage change between baseline and week 12 was not significantly different between treatment groups ($P = 0.40$), nor was maximum PINP percentage change ($P = 0.13$). Mean PINP percentage change between baseline and week 12 was not significantly different between PPA responders and nonresponders ($P = 0.55$), nor was maximum PINP percentage change ($P = 0.26$). Patients with ≥20% VAS response had significantly lower baseline PINP concentrations when compared to patients with <20% VAS response (Table 1). Similarly, patients with ≥20% PPA response had lower baseline PINP concentrations when compared to patients with <20% PPA response (Table 1). The percentage change of PINP levels between baseline and week 12 is outlined in Fig. 1.

A significant negative correlation was found between baseline PINP serum concentrations and maximum pain response assessed either by the VAS ($r = -0.59$, $P < 0.0001$) or by the PPA score ($r = -0.30$, $P = 0.02$). The time course of pain response as assessed either by the VAS or the PPA score is compared between patients with a low or high baseline PINP concentration in Fig. 2. A significant negative correlation was found between baseline PINP serum concentrations and duration of pain response ($r = -0.46$, $P = 0.0001$). Accordingly, a high baseline serum PINP concentration (highest when compared to the lower two tertiles) was significantly associated with a shorter duration of pain response (Fig. 3). After three treatment cycles or approximately 2 months of treatment, the proportion of patients with ongoing pain response was 18% in patients with a high baseline PINP concentration when compared to 45% in patients with a low PINP concentration ($P < 0.0001$).

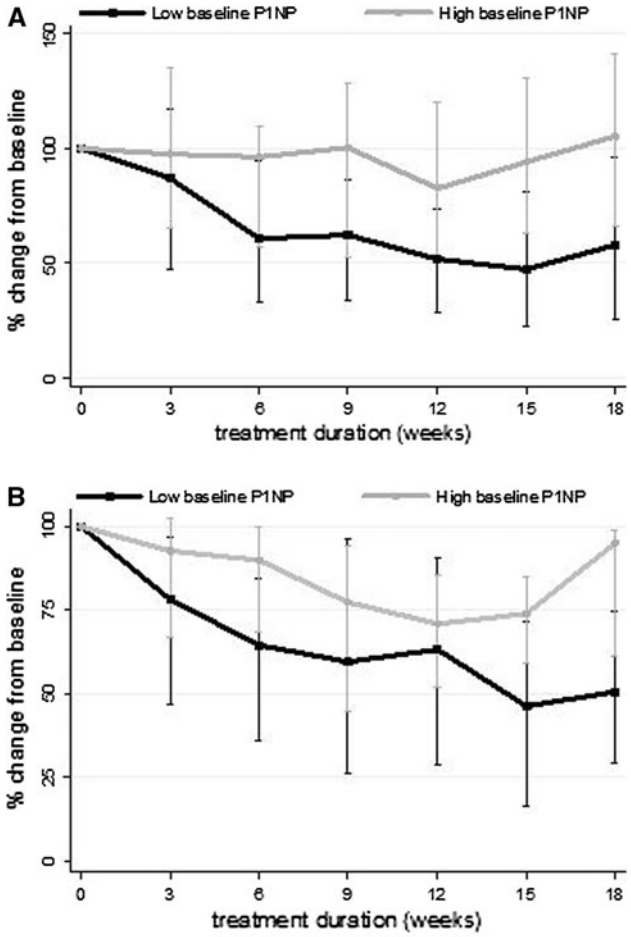

Fig. 2 Time course of pain response [pain intensity (**a**) and pain frequency (**b**) on the VAS] as a percentage change from baseline ±SEM for patients with a low baseline PINP serum concentration (lowest tertile) compared to patients with a high baseline PINP serum concentration (higher two tertiles)

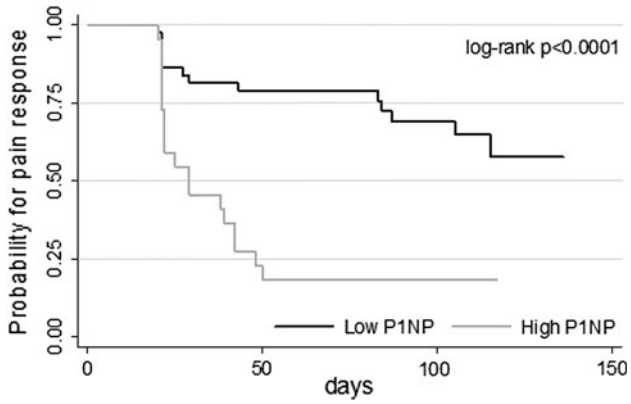

Fig. 3 Kaplan–Meier curves for the duration of pain response. Patients with low baseline PINP serum concentrations (lowest tertile) compared to patients with high baseline PINP serum concentrations (higher two tertiles)

Table 2 Predictors for pain response by the VAS using univariate and multivariate logistic regression analysis

Pain response by the VAS	Univariate		Multivariate	
Covariate	OR (95%-CI)	*P*-value	OR (95%-CI)	*P*-value
Baseline PINP serum concentration				
Low tertile	2.8 (1.0–8.3)	.05	3.0 (0.9–10.2)	.08
Higher two tertiles	Ref		Ref	
Baseline bone alkaline phosphatase				
Low tertile	2.6 (0.9–7.3)	.08	1.9 (0.5–7.2)	0.35
Higher two tertiles	Ref		Ref	
Patient gender				
Female	Ref		Ref	
Male	1.4 (.4–4.7)	.55	1.4 (.2–10.3)	.73
Patient age				
<60 years	Ref		Ref	
≥60 years	1.0 (.4–2.6)	1.0	.75 (.2–2.5)	.65
ECOG-PS				
0–1	3.9 (1.4–10.7)	.009	5.1 (1.4–18.1)	.01
2–4	Ref		Ref	
Primary diagnosis				
Breast cancer	Ref		Ref	
Multiple myeloma	4.1 (1.1–14.8)	.03	2.1 (.4–12.0)	.38
Others	1.01 (.2–5.14)	.99	.6 (.06–6.2)	.68
Randomisation				
60 mg pamidronate	Ref		Ref	
90 mg pamidronate	1.1 (.4–2.9)	.24	1.3 (.4–4.0)	.67
Anticancer treatment				
None	Ref		Ref	
Chemotherapy	1.6 (.5–5.3)	.41	2.3 (.5–10.7)	.30
Endocrine treatment	2.3 (.3–17.8)	.44	2.1 (.2–24.5)	.56

OR Odds-ratio, *Ref* reference, *CI* confidence interval, *PS* performance score, *PINP* N-telopeptide of type I collagen, *VAS* visual-analog-scale

In the multivariate logistic regression model, no significant predictors were found for PPA response, nor for the duration of pain response. ECOG-PS < 2 and a low baseline PINP concentration were favorable predictors of VAS-response (Table 2). The predictive value of baseline PINP concentrations was independent of other covariates such as bone alkaline phosphatase, patient gender, age, disease entity, specific anticancer treatment such as endocrine treatment or chemotherapy, and pamidronate treatment group. Forty-five out of the 70 patients (64%) experienced a SRE, including radiotherapy in 37 cases, surgery to the bone in three cases, pathological fractures in four cases and radioisotope treatment in a single case. Randomization to the 90 mg pamidronate treatment group, age < 60 years and a low baseline serum PINP concentration were independent favorable predictors for a longer time interval to first SRE. Kaplan–Meier curves for the time-to-first-SRE in patients with a high when compared to those with a low or intermediate baseline serum PINP concentration are shown in Fig. 4. At 6 months from randomisation, the proportion of patients with no SRE was 20% in patients with a high baseline PINP concentration when compared to 74% in patients with a low PINP concentration ($P < 0.008$). Sensitivity of a low baseline PINP serum concentration for no SRE at 1 year from randomization was 75% (15 out of 20 patients), specificity 82% (27 out of 33 patients), with 17 patients censored for sensitivity analysis (death before 12 months from randomisation without any SRE). More patients with a favorable pain response as assessed by the PPA score were free from SRE at 6 (75 vs. 45%) and 12 months (33% vs. 8%), but this did not reach statistical significance ($P = 0.14$ by the log-rank test).

Discussion

The skeleton is the preferred site of metastases for many solid tumors, with the prevalence for MBD being highest in breast and prostate cancer (65–75%) followed by thyroid (60%), lung (40%) and bladder cancer (30–40%) [19]. We showed for the first time that baseline PINP serum concentrations are predictive for early pain response and skeletal

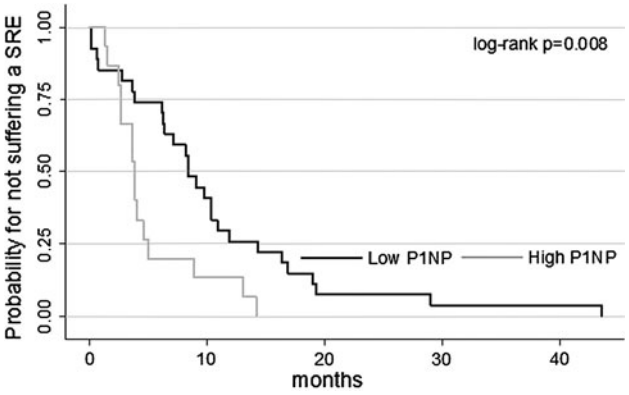

Fig. 4 Kaplan–Meier curves for the time to first skeletal-related event (SRE), including pathologic fracture, spinal cord compression and surgery to the bone or radiation to the bone (including radioisotopes). Patients with low baseline PINP serum concentrations (lowest tertile) compared to patients with high baseline PINP serum concentrations (higher two tertiles)

outcome (SRE) in patients with advanced MBD on antiresorptive treatment, and this was independent of other covariates such as patient gender, age, primary diagnosis and pamidronate treatment group (Table 2). These results are of particular interest, as the unselective use of bone-targeted agents puts patients at risk for severe morbidity, and individualized treatment is urgently needed. The reasons for choosing PINP over other bone turnover markers were the fact that PINP in serum has been shown to strongly correlate with metastatic spread in osseous metastatic breast cancer [20] and that it has been suggested that serum bone formation markers might exhibit less intra-individual variability when compared to urinary markers [21]. In the study by Pollmann and colleagues, baseline serum samples of 51 patients with metastatic breast cancer undergoing chemotherapy were investigated [20]. Overall, baseline levels of PINP were significantly higher in patients with bone metastases when compared to those without bone metastases (92.8 µg/l vs. 63.2 µg/l, $P = 0.04$) and showed a close correlation with treatment response. Importantly, osteocalcin and CTX did not show a similar sensitivity for the surveillance of bone metastases in this study [20]. Leary and colleagues studied CTX and PINP levels in patients with osteoporosis and nonosteoporotic individuals to assess long-term stability of the analytes and compare individual patient responses following antiresorptive treatment [22]. This study validated PINP as a predictor for antiresorptive treatment in osteoporosis, and confirmed excellent long-term precision in samples stored at −70°C [22]. Furthermore, the advantage of using a bone formation marker from serum such as PINP includes its ease of sampling and analysis, and its high sensitivity to changes in bone turnover, as shown in the present study and in former reports [23]. A potential disadvantage of bone turnover markers from serum includes its vulnerability to circadian variability that is at least in part compensated by urine sampling over several hours.

Along with analgesics, bisphosphonate therapy is a major factor contributing to the preservation of mobility, social functioning and quality-of-life in patients with progressive MBD [24–40]. By doing so, bisphosphonates have been shown to reduce opioid-resistant bone pain and maintain it at lower levels over the course of progressive MBD [31]. At present, amino-bisphosphonates are recommended for patients with metastatic bone disease from breast cancer, and zoledronic acid for patients with other solid tumors as primary disease, to prevent, reduce and delay cancer-related skeletal complications in these patients [41]. Although zoledronic acid is seen as more effective in terms of bone remineralization in comparison with pamidronate, zoledronic acid and pamidronate showed similar activity in pain response and prevention of SRE in patients with prostate cancer [42] and multiple myeloma [43]. In patients with osteolytic bone metatases from breast cancer, zoledronic acid was more effective than pamidronate 90 mg in reducing SRE in some studies [44], but not in others [45]. Therefore, pamidronate is still a viable treatment option for patients with MBD.

Presently, a multitude of bone turnover markers have been described, and some of them have been tested in clinical studies of bisphosphonates in MBD [8, 9, 46]. In the phase III study by Body and colleagues, the effect of oral ibandronate 50 mg/day ($n = 137$) and iv. zoledronic acid 4 mg every 4 weeks ($n = 138$) on bone markers was compared [46]. The primary outcome of this study was mean percentage change in serum levels of cross-linked C-terminal telopeptide of type I collagen (S-CTX) after 12 weeks of study treatment. As a result, both oral ibandronate and intravenous zoledronic acid decreased S-CTX levels to a similar amount (mean 76% vs. 73%, respectively). Serum PINP concentrations were also assessed in the latter study, and again both oral ibandronate and intravenous zoledronic acid decreased PINP levels to a similar amount (mean 47% vs. 39%, respectively). No difference in bone pain was found between the two treatment groups in the study by Body and colleagues, but the individual association between bone turnover markers and pain response was not outlined. Vinholes and colleagues analyzed various bone resorption markers including PINP and CTX in 32 patients undergoing treatment with i.v. pamidronate 90 mg or clodronate 1'500 mg for hypercalcemia of malignancy [23]. Both serum PINP and urinary CTX showed the most extended drops until approximately day 7 after the administration of the bisphosphonate, followed by a gradual increase in the marker. Pamidronate was more effective in suppressing PINP and CTX concentrations [23]. In a more recent study by Agrawal and colleagues, 14 patients with

locally advanced breast cancer and no evidence for bone metastases received monthly fulvestrant and sequential analysis of bone-specific alkaline phosphatase, PINP and CTX [47]. No significant changes in bone markers were found over a period of 18 months, and this was related to a prolonged therapeutic benefit from fulvestrant [47]. Presently, there is very limited data on the predictive value of bone turnover markers for pain response in patients receiving bisphosphonate treatment, and the use of markers of bone resorption has mainly been limited by their assessment in urine samples. Accordingly, the use of bone markers for individualizing bone-targeted treatment cannot yet be recommended in clinical routine, but the large ongoing BISMARK study (BISphosphonate therapy directed by bone resportion MARKers) is actually addressing the issue of using bone resorption markers in the timing of bisphosphonate treatment [48].

The limitations of the present study include the different doses of pamidronate that might have influenced study results, potential stability issues with regards to PINP bioanalysis, heterogeneity introduced by the different tumor types, potential circadian variability of serum PINP concentrations [49], a potential bias due to the fact that 77% of the patients received nonpamidronate anticancer treatment, and the fact that zoledronic acid is frequently given in place of pamidronate for MBD in these days. With regards to the first point, serum PINP concentrations were not different between treatment groups, and the original publication showed no difference in pain response between the higher and lower dose of pamidronate [15]. With regards to the second point, medium-term stability data have been published for PINP in samples stored at −80°C by Garnero and colleagues [11], and final results of time–concentration data of serum PINP support the internal validity for the results as reported in this study. With regards to the third point, heterogeneity introduced by including various tumor types has been limited as the study only included patients with osteolytic MBD, and the fact that a potential predictor for the treatment of MBD should have some general applicability in patients with cancer. Circadian variability of PINP serum concentrations has been described by Ahmad and colleagues [49] in 14 patients with osteoporosis. In the study by Ahmad and colleagues, serum PINP concentrations varied with the activity of endogenous parathyroid hormone and followed a circadian rhythm [49]. To account for nonpamidronate anticancer treatment, potential predictive markers of skeletal morbidity underwent multivariate logistic regression analysis as outlined in Table 2. With regards to the last point, pamidronate has been shown to be equally effective in treating pain from MBD in patients with advanced prostate cancer [42] and myeloma [43], while there are some controversial results for the superiority of zoledronic acid in patients with MBD from breast cancer [44, 45]. In conclusion, this study shows that serum PINP is a significant predictor for skeletal morbidity in patients with MBD on pamidronate treatment. Prospective validation of PINP in patients with MBD to assess the prognosis or individualize bone-targeted treatment is justified.

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Conflict of interest B.Thürlimann has received reimbursement for Advisory Board activities from GSK and Roche, holds stocks of Novartis and Rochen, and received honoraria and travel grants related to educational activities from AstraZeneca, Novartis, Janssen-Cilag, BMS, Sanofi-Aventis, Phillips Group, Prime Oncology, GSK and EliLilly. No Conflict of interest declared by the other authors.

Reference

1. Mundy GR (2002) Metastasis to bone: causes, consequences and therapeutic opportunities. Nat Rev Cancer 2(8):584–593
2. Janjan N (2001) Bone metastases: approaches to management. Semin Oncol 28(4 Suppl 11):28–34
3. Vinholes J, Coleman R, Eastell R (1996) Effects of bone metastases on bone metabolism: implications for diagnosis, imaging and assessment of response to cancer treatment. Cancer Treat Rev 22:289–331
4. Lipton A, Berenson JR, Body JJ et al (2006) Advances in treating metastatic bone cancer: summary statement for the First Cambridge Conference. Clin Cancer Res 12(20 Pt 2):6209s–6212s
5. Coleman RE (2008) Risks and benefits of bisphosphonates. Br J Cancer 98(11):1736–1740
6. Fizazi K, Bosserman L, Gao G et al (2009) Denosumab treatment of prostate cancer with bone metastases and increased urine N-telopeptide levels after therapy with intravenous bisphosphonates: results of a randomized phase II trial. J Urol 182(2):509–515
7. Brown JE, McCloskey EV, Dewar JA et al (2007) The use of bone markers in a 6-week study to assess the efficacy of oral clodronate in patients with metastatic bone disease. Calcif Tissue Int 81(5):341–351
8. Coleman RE, Major P, Lipton A et al (2005) Predictive value of bone resorption and formation markers in cancer patients with bone metastases receiving the bisphosphonate zoledronic acid. J Clin Oncol 23(22):4925–4935
9. Cook RJ, Coleman R, Brown J et al (2006) Markers of bone metabolism and survival in men with hormone-refractory metastatic prostate cancer. Clin Cancer Res 12(11 Pt 1):3361–3367
10. Engler H, Koeberle D, Thuerlimann B et al (1998) Diagnostic and prognostic value of biochemical markers in malignant bone disease: a prospective study on the effect of bisphosphonate on pain intensity and progression of malignant bone disease. Clin Chem Lab Med 36(11):879–885
11. Garnero P, Vergnaud P, Hoyle N (2008) Evaluation of a fully automated serum assay for total N-terminal propeptide of type I collagen in postmenopausal osteoporosis. Clin Chem 54(1):188–196
12. McCaig FM, Renshaw L, Williams L et al (2010) A study of the effects of the aromatase inhibitors anastrozole and letrozole on bone metabolism in postmenopausal women with estrogen receptor-positive breast cancer. Breast Cancer Res Treat 119(3):643–651
13. Lüftner D, Jozereau D, Schildhauer S et al (2005) PINP as serum marker of metastatic spread to the bone in breast cancer patients. Anticancer Res 25(3A):1491–1499

14. Diaz-Martin MA, Traba ML, de la Piedra C et al (1999) Aminoterminal propeptide of type I collagen and bone alkaline phosphatase in the study of bone metastases associated with prostatic carcinoma. AScand J Clin Lab Invest 59(2):125–132
15. Koeberle D, Bacchus L, Thuerlimann B et al (1999) Pamidronate treatment in patients with malignant osteolytic bone disease and pain: a prospective randomized double-blind trial. Support Care Cancer 7(1):21–27
16. Gessner U, Koeberle D, Thuerlimann B et al (2000) Economic analysis of terminal care for patients with malignant osteolytic bone disease and pain treated with pamidronate. Support Care Cancer 8(2):115–122
17. Brandt J, Krogh TN, Jensen CH et al (1999) Thermal instability of the trimeric structure of the N-terminal propeptide of human procollagen type I in relation to assay technology. Clin Chem 45(1):47–53
18. Purohit OP, Anthony C, Radstone CR et al (1994) High-dose intravenous pamidronate for metastatic bone pain. Br J Cancer 70(3):554–558
19. Coleman RE (2001) Metastatic bone disease: clinical features, pathophysiology and treatment strategies. Cancer Treat Rev 27(3):165–176
20. Pollmann D, Siepmann S, Geppert R et al (2007) The amino-terminal propeptide (PINP) of type I collagen is a clinically valid indicator of bone turnover and extent of metastatic spread in osseous metastatic breast cancer. Anticancer Res 27(4A):1853–1862
21. Looker A, Bauer D, Chesnut C III et al (2000) Clinical use of biochemical markers of bone remodelling: Current status and future directions. Osteoporos Int 11:467–480
22. Leary E (2005) Serum CTX and P1NP by Roche Elecsys as Theranostics in the Treatment of Osteoporosis. J Bone Mineral Res 20(suppl.1):S227
23. Vinholes J, Guo CY, Purohit OP et al (1997) Evaluation of new bone resorption markers in a randomized comparison of pamidronate or clodronate for hypercalcemia of malignancy. J Clin Oncol 15(1):131–138
24. Mancini I, Dumon JC, Body JJ (2004) Efficacy and safety of ibandronate in the treatment of opioid-resistant bone pain associated with metastatic bone disease: a pilot study. J Clin Oncol 22(17):3587–3592
25. Heidenreich A, Hofmann R, Engelmann UH (2001) The use of bisphosphonate for the palliative treatment of painful bone metastasis due to hormone refractory prostate cancer. J Urol 165(1):136–140
26. Weinfurt KP, Li Y, Castel LD et al (2005) The significance of skeletal-related events for the health-related quality of life of patients with metastatic prostate cancer. Ann Oncol 16(4):579–584
27. Heidenreich A, Ohlmann C, Body JJ (2004) Ibandronate in metastatic bone pain. Semin Oncol 31(5 Suppl 10):67–72
28. Body JJ, Diel IJ, Lichinitzer M et al (2004) Oral ibandronate reduces the risk of skeletal complications in breast cancer patients with metastatic bone disease: results from two randomised, placebo-controlled phase III studies. Br J Cancer 90(6):1133–1137
29. Body JJ, Diel IJ, Bell R et al (2004) Oral ibandronate improves bone pain and preserves quality of life in patients with skeletal metastases due to breast cancer. Pain 111(3):306–312
30. Saad F, Olsson C, Schulman CC (2004) Skeletal morbidity in men with prostate cancer: quality-of-life considerations throughout the continuum of care. Eur Urol 46(6):731–739
31. Gralow J, Tripathy D (2007) Managing metastatic bone pain: the role of bisphosphonates. J Pain Symptom Manage 33(4):462–472
32. Wardley A, Davidson N, Barrett-Lee P et al (2005) Zoledronic acid significantly improves pain scores and quality of life in breast cancer patients with bone metastases: a randomised, crossover study of community vs hospital bisphosphonate administration. Br J Cancer 92(10):1869–1876
33. Weinfurt KP, Castel LD, Li Y et al (2004) Health-related quality of life among patients with breast cancer receiving zoledronic acid or pamidronate disodium for metastatic bone lesions. Med Care 42(2):164–175
34. Clemons M, Dranitsaris G, Ooi W et al (2008) A Phase II trial evaluating the palliative benefit of second-line oral ibandronate in breast cancer patients with either a skeletal related event (SRE) or progressive bone metastases (BM) despite standard bisphosphonate (BP) therapy. Breast Cancer Res Treat 108(1):79–85
35. Diel IJ, Body JJ, Lichinitser MR et al (2004) Improved quality of life after long-term treatment with the bisphosphonate ibandronate in patients with metastatic bone disease due to breast cancer. Eur J Cancer 40(11):1704–1712
36. Hong SJ, Cho KS, Cho HY et al (2007) A prospective, multicenter, open-label trial of zoledronic acid in patients with hormone refractory prostate cancer. Yonsei Med J 48(6):1001–1008
37. Kretzschmar A, Wiege T, Al-Batran SE et al (2007) Rapid and sustained influence of intravenous zoledronic Acid on course of pain and analgesics consumption in patients with cancer with bone metastases: a multicenter open-label study over 1 year. Support Cancer Ther 4(4):203–210
38. Mystakidou K, Katsouda E, Parpa E et al (2006) A prospective randomized controlled clinical trial of zoledronic acid for bone metastases. Am J Hosp Palliat Care 23(1):41–50
39. Ripamonti C, Fagnoni E, Campa T et al (2007) Decreases in pain at rest and movement-related pain during zoledronic acid treatment in patients with bone metastases due to breast or prostate cancer: a pilot study. Support Care Cancer 15(10):1177–1184
40. Small EJ, Smith MR, Seaman JJ et al (2003) Combined analysis of two multicenter, randomized, placebo-controlled studies of pamidronate disodium for the palliation of bone pain in men with metastatic prostate cancer. J Clin Oncol 21(23):4277–4284
41. Aapro M, Abrahamsson PA, Body JJ et al (2008) Guidance on the use of bisphosphonates in solid tumours: recommendations of an international expert panel. Ann Oncol 19(3):420–432
42. Sherer JT, Adamus AT (2007) Outcomes of patients with prostate cancer receiving zoledronic acid or pamidronate for prevention of skeletal-related events. Pharmacotherapy 27(2):207–217
43. Rosen LS, Gordon D, Kaminski M et al (2003) Long-term efficacy and safety of zoledronic acid compared with pamidronate disodium in the treatment of skeletal complications in patients with advanced multiple myeloma or breast carcinoma: a randomized, double-blind, multicenter, comparative trial. Cancer 98(8):1735–1744
44. Rosen LS, Gordon DH, Dugan W et al (2004) Zoledronic acid is superior to pamidronate for the treatment of bone metastases in breast carcinoma patients with at least one osteolytic lesion. Cancer 100(1):36–43
45. Rosen LS, Gordon D, Kaminski M et al (2001) Zoledronic acid versus pamidronate in the treatment of skeletal metastases in patients with breast cancer or osteolytic lesions of multiple myeloma: a phase III, double-blind, comparative trial. Cancer J 7(5):377–387
46. Body JJ, Lichinitser M, Tjulandin S et al (2007) Oral ibandronate is as active as intravenous zoledronic acid for reducing bone turnover markers in women with breast cancer and bone metastases. Ann Oncol 18(7):1165–1171
47. Agrawal A, Hannon RA, Cheung KL et al (2009) Bone turnover markers in postmenopausal breast cancer treated with fulvestrant - A pilot study. The Breast 18:204–207
48. Gainford MC, Dranitsaris G, Clemons M (2005) Recent developments in bisphosphonates for patients with metastatic breast cancer. BMJ 330(7494):769–773
49. Ahmad AM, Hopkins MT, Fraser WD et al (2003) Parathyroid hormone secretory pattern, circulating activity, and effect on bone turnover in adult growth hormone deficiency. Bone 32(2): 170–179