Tartrate-resistant acid phosphatase (TRAP) as a serum marker for bone resorption in breast cancer patients with bone metastases

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Summary

Background: A novel immunoassay specific for the osteoclast-produced tartrate-resistant acid phosphatase TRAP isoform 5b was developed some years ago. By means of this assay, the usefulness of serum TRAP in monitoring the response to palliative treatment with clodronate in breast cancer patients with bone metastases was studied. Serum TRAP was examined for correlation with the activity of bone osteoclasts in these patients. *Materials and Methods:* Seventeen patients took part in this study taking 1600 mg clodronate daily as a tablet for five months. Eleven of these patients were evaluated. *Results:* TRAP activity correlated well with the grade of bone metastases and with the number of locations in the body. During the therapy with clodronate, TRAP activity in serum decreased. *Conclusions:* We conclude that the measurement of TRAP is useful in monitoring treatment with bisphosphonate clodronate in patients with bone metastatic breast cancer.

Key words: Tartrate-resistant acid phosphatase (TRAP); Bone metastases; Clodronate.

Introduction

Bone metastases during metastatic breast cancer disease are common. Autopsy studies have shown that 70-85% of all women who died of metastatic breast cancer had skeletal metastasis [1]. One out of every four women who are diagnosed with breast cancer will suffer from bone metastases. In the United States where 180,000 women each year are diagnosed with a malignant breast tumour, 40,000-45,000 could benefit from bisphophonate therapy each year.

Patients suffer an ongoing risk of skeletal complications that can have a significant impact on their quality of life. Bone metastases lead to typical complications like pain, fractures and nerve compressions after fractures in the spine. Characteristics of the terminal phase of the illness are hypercalcemia and bone marrow carcinosis.

Studies have shown that the development of bone metastases from breast cancer is facilitated by the release of substances from tumour cells that activitate osteclasts to lead to local osteolysis [2]. Use of agents such as bisphosphonates like clodronate inhibits tumour-induced osteolysis in vitro and prevents bone destruction and hypercalcemia in vivo [3].

Several studies pointed out that therapy with clodronate reduces the incidence of hypercalcemia and pathological bone fractures [4]. Kanis *et al*. showed that in breast cancer patients without obvious bone involvement, clodronate significantly reduced the risk of developing bone metastases [5]. In 2002, Powles *et al*. demonstrated that clodronate significantly reduced the occurrence of bone metastases with primary operable breast cancer during the medication period [6]. There was even a significant reduction in mortality for patients who were randomized to clodronate compared to a placebo group [6]. Dando and Wiseman describe in a review that clodronate was extensively used in patients with advanced breast cancer and was tolerated well. In patients with primary breast cancer clodronate was the only bisphosphonate which improved the survival rate and reduced the incidence of bone metastases in randomised controlled trials [7].

Tartrate-resistant phospatase (TRAP) is an enzyme which could be used as a marker of the osteoclasts which are bone resorbant. There are two forms of this enzyme: isoform 5a and 5b; 5b is the active form and is specific for osteoclasts, and is detectable and measureable in serum.

TRAP belongs to the group of most proposed markers for assessing the state of skeletal turnover and in particular of bone resorption [8]. The study of Scarnecchia et al. demonstrated in 1991 that the measurement of serum TRAP activity may be useful in assessing bone turnover [9]. In their study, the TRAP concentration in healthy subjects was compared to patients with metabolic bone diseases, including seven patients with bone metastases secondary to breast cancer, and found to be significantly lower [9].

Therefore we hypothesised that the measurement of TRAP could be useful and helpful in monitoring bone resorption at any stage of disease by indicating if the bisphosphonate therapy with clodronate is working. TRAP

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Fig. 1

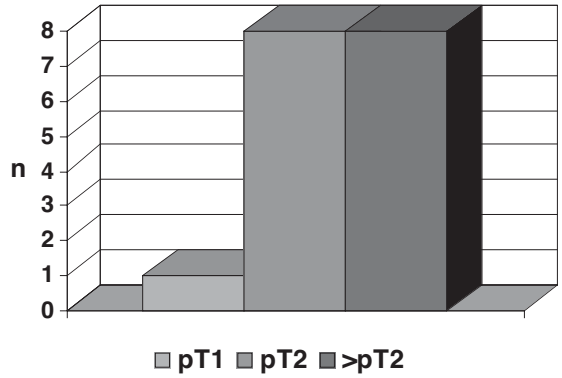


Fig. 2

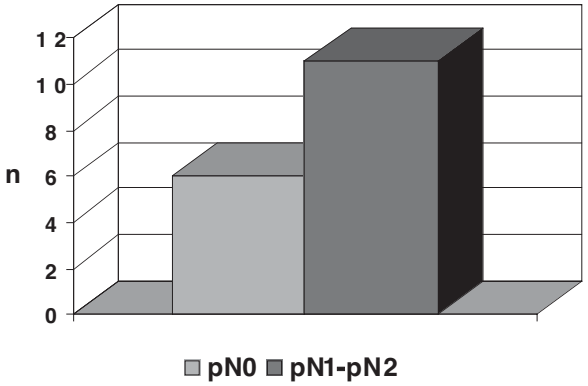


Fig. 3

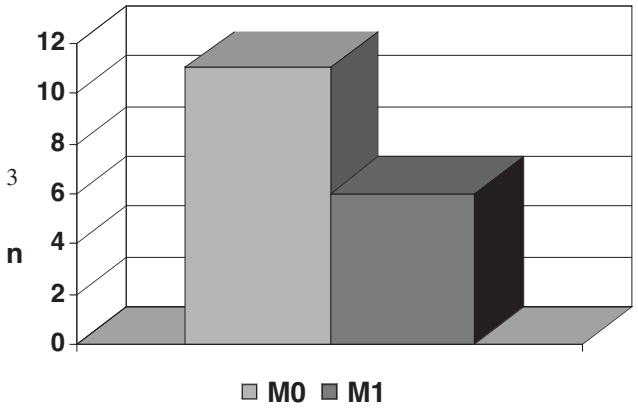


Fig. 4

Figures 1-2. — Tumour stage at time of first diagnosis (n = number of patients).
Figure 3. — State of metastases at time of first diagnosis.
Figure 4. — Hormone receptors.

may help determine the quantitative grade of bone resorption in bone metastatic breast cancer patients at the time of routine blood collection.

Our primary study aim was to determine the clinical relevance of the measurement of TRAP in monitoring of bisphosphonate therapy in patients with metastatic breast cancer.

Patients and Methods

Seventeen patients admitted to the Department of Obstetrics and Gynaecology of the University Hospital of Saarland, Germany took part in this study. The median age of the patients was 62.5 years. The serum results of 11 patients were evaluable. All subjects had symptomatic or asymptomatic progressive bone metastases and had not received bisphosphonate therapy before. All patients were advised of the nature and purpose of the study before giving their informed written consent to participate. The study was approved by the ethics committee of the university. Patients were free of psychiatric problems and had sufficient liver and kidney function. They gave their consent to take one tablet of 1600 mg clodronate daily.

Before starting the therapy serum analysis of TRAP was taken; this was repeated every 14 days. At the end of the study period (five months of therapy) a conventional analysis of bone metastases was carried out (X-ray or bone scanning).

Results

Patient characteristics

Figures 1-4 show tumor stage and metastases at the first diagnoses and hormone receptor status.

Bone metastases

Figures 5 and 6 show the forms of the bone metastases and the symptoms patients had when metastases were diagnosed. Out of 17 patients, there were four patients who only had bone metastases.

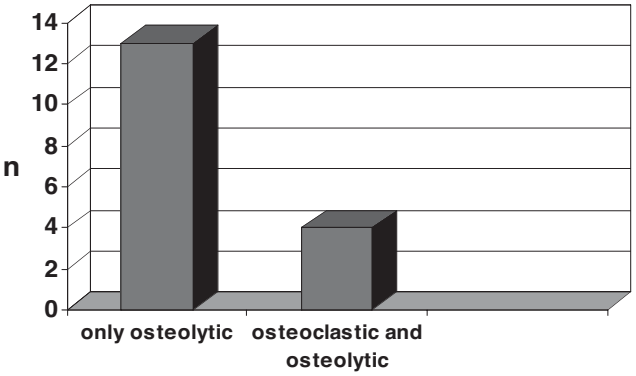


Figure 5. — Forms of bone metastases.

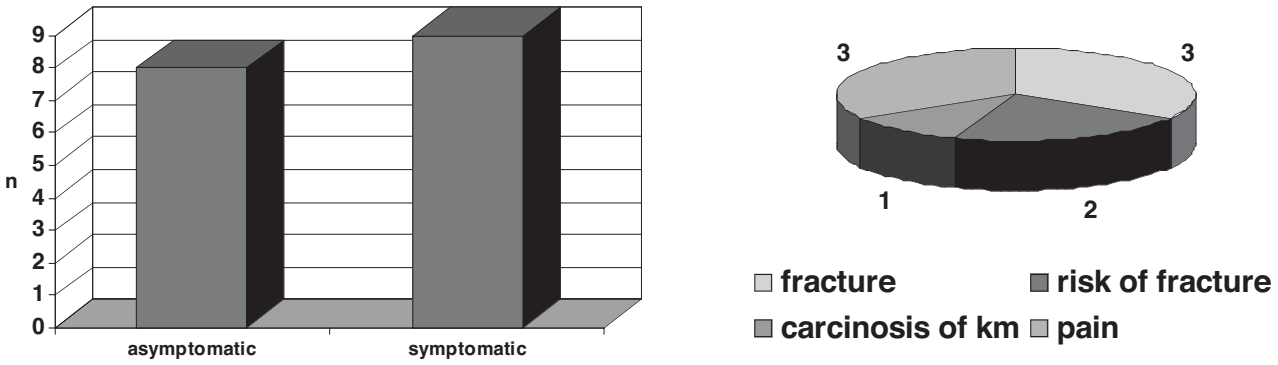


Figure 6. — Symptoms and complications of bone metastases.

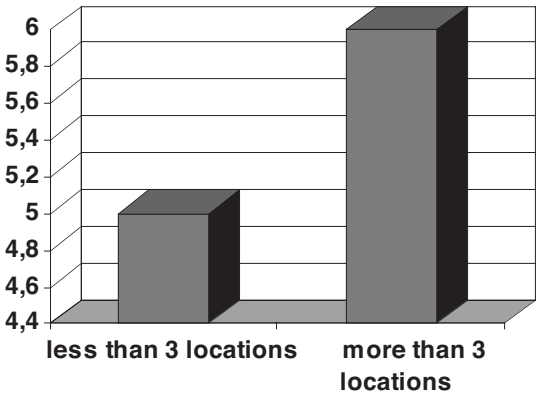


Figure 7. — Number of bone metastasis locations.

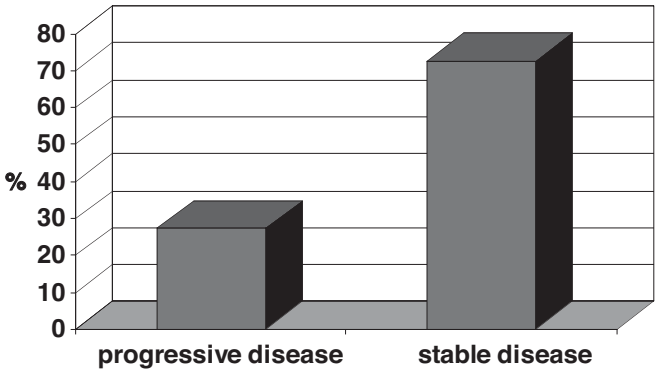


Figure 8. — Monitoring of the bone metastases.

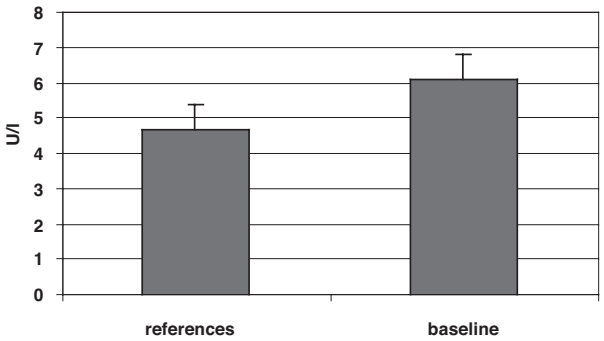


Figure 9. — Mean values of TRAP before treatment.

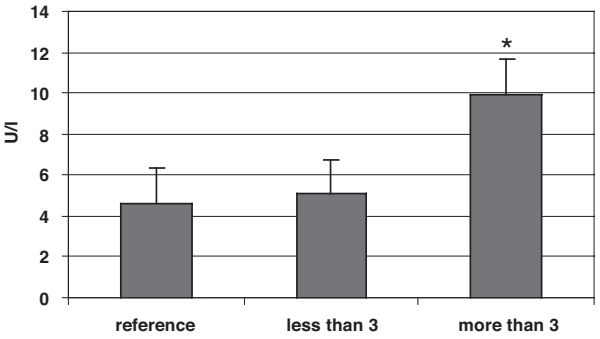


Figure 10. — Mean baseline values of TRAP according to number of metastatic locations (* $p < 0.05$).

In Figures 7 and 8 the number of locations of bone metastases and the state of the illness before and after therapy of the patients (n = 11) who could be evaluated are shown; 3/11 patients had progressive disease, 8/11 showed stable disease.

The following figures indicate the activity of TRAP in serum before and during clodronate therapy. The reference value for serum TRAP activity is 3.43 IU/ml for premenopausal women and 4.63 IU/ml in postmenopausal women. Our study patients were all postmenopausal.

Figure 9 shows the baseline value of TRAP before the start of treatment. As the figure shows, baseline mean values increased without reaching statistical significance in our patients. The mean values of serum TRAP in patients with more than three locations of bone metastases were 9.95 IU/ml and significantly higher in comparison to normal values and to patients with less than three locations of bone metastases (mean values: 5.06 IU/ml).

The following five figures (Figures 11-15) give information about the development of TRAP during the time of therapy. Regarding all patients (as well as the two subgroups) there was a constant decrease in TRAP activity. Reduction of TRAP was the highest in patients with more than three locations of bone metastases.

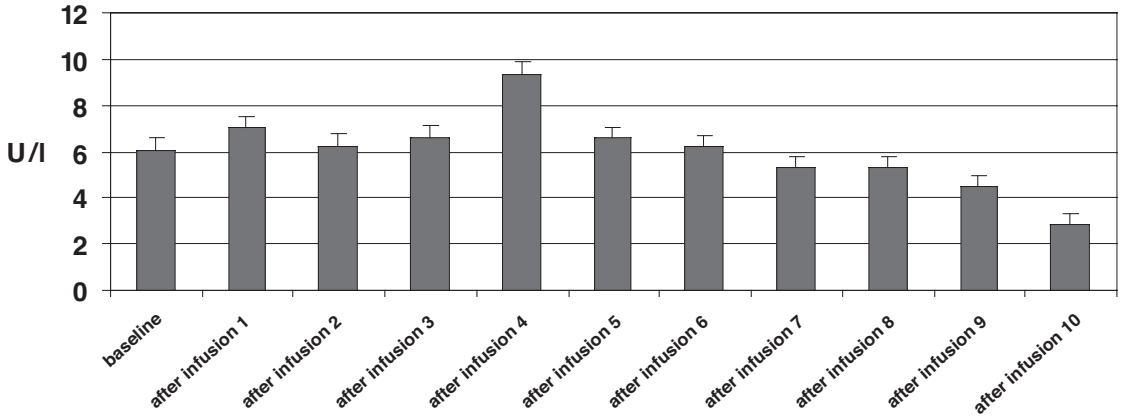


Figure 11. — Serum in TRAP levels in all patients during the treatment.

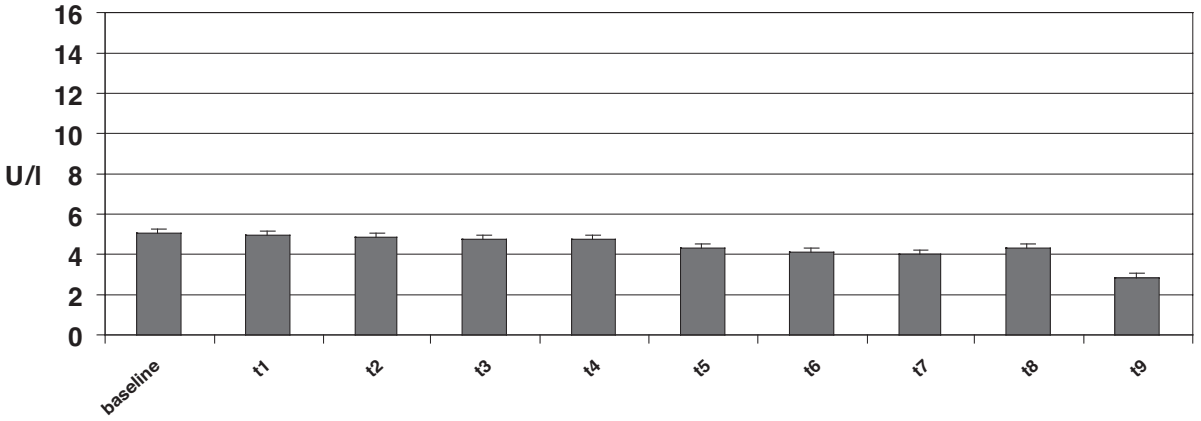


Figure 12. — Serum TRAP levels in all patients with less than three locations of bone metastases.

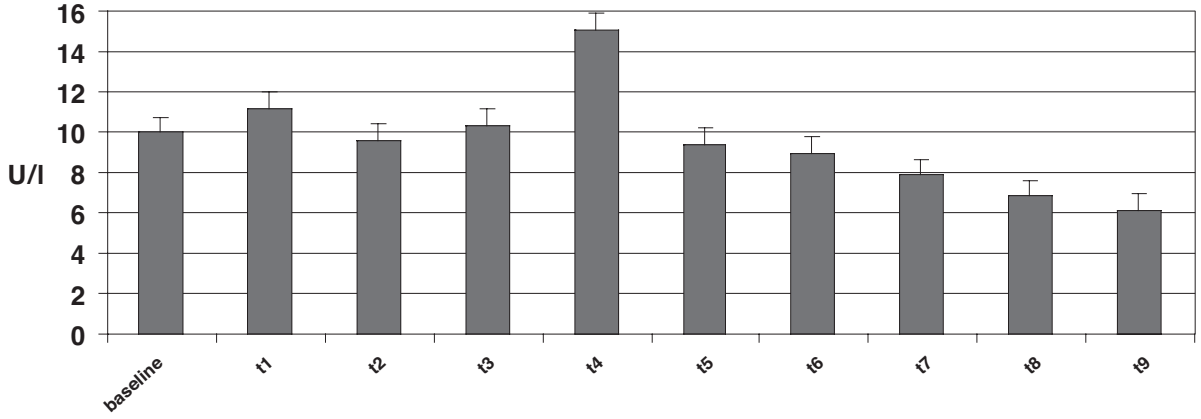


Figure 13. — Changes of TRAP in patients with more than three locations of bone metastases.

TRAP at different stages of therapy (Figures 16-18)

The analysis of TRAP at different stages of therapy (Figures 16-18) show a significant reduction of TRAP concentration in the serum at the third month of therapy in patients with more than three locations of bone metastases ($p < 0.05$). In all patients and in the group of patients with less than three locations of bone metastases there was a reduction in TRAP activity (Figures 17 and 18) which was not significant.

Discussion

Our study showed that the evaluation of TRAP gives useful information about bone metastases in breast cancer in the primary diagnosis as well as a marker of monitoring therapy with clodronate. Continous measurement of TRAP is necessary to evaluate the success of clodronate therapy. Like a tumour marker which is evaluated in a specific period of time, regression, progression or stable disease can be diagnosed. Capeller *et al*. demonstrated in

Fig. 14

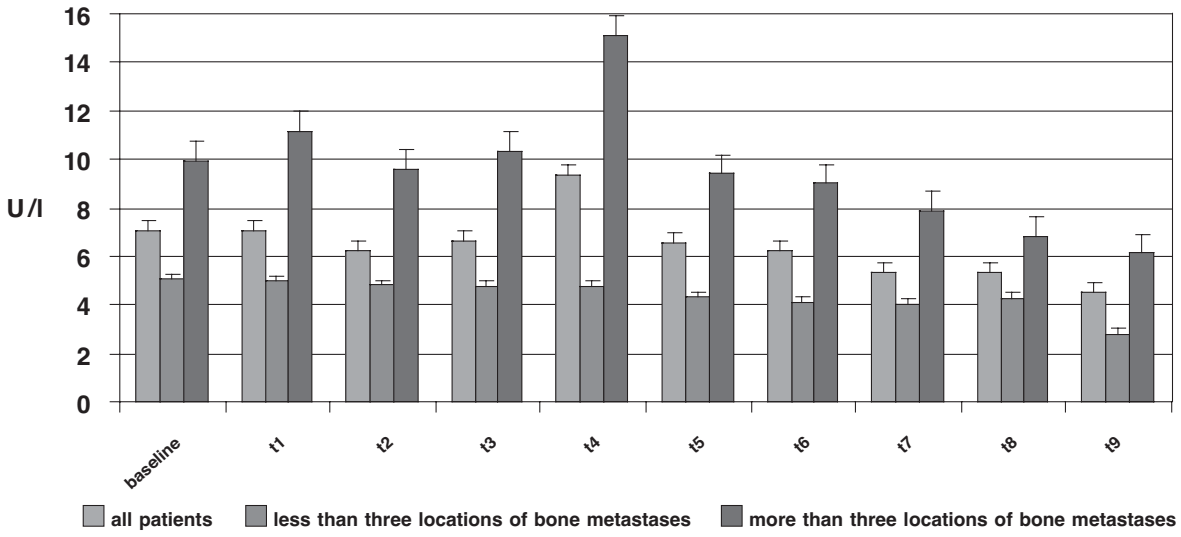
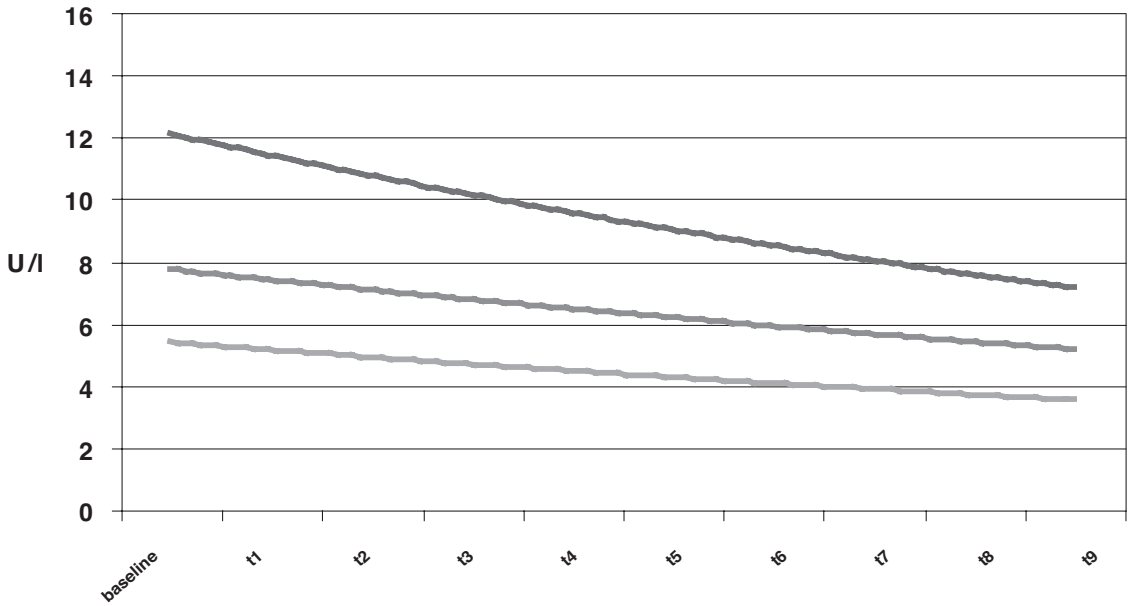


Fig. 15



Figures 14-15. — Data of all patients and subgroups.

2003 that TRAP levels decline under bisphosphonate therapy when no progression is detectable. When progress of the bone metastases occurs, TRAP levels rise again [10]. We confirmed these data showing a reduction of TRAP during therapy with clodronate, independent of the number of locations of bone metastases.

Recently Chao *et al*. showed that TRAP is a useful serum marker for extensive bone metastases in breast cancer patients. In 168 breast cancer patients, including 81 who were newly diagnosed with early breast cancer, 20 with extraosseous metastasis, 24 with limited bone metastases and 43 patients with extensive bone metastases TRAP activity was measured. TRAP was significantly elevated in patients with extensive bone metastases compared to all other groups ($p < 0.0001$) [11].

Lyubimova *et al*. showed in 2004 that serum activity of TRAP in patients with breast cancer having bone metastases was much higher than in healthy donors and patients without skeletal injuries. We confirmed their results that TRAP concentration in serum of patients with multiple bone metastases due to breast cancer surpassed that in patients with single bone metastases. Diagnostic sensitivity and specificity of TRAP as a marker of skeletal metastases in patients with breast cancer were 82% and 87%, respectively. They concluded that the detection of TRAP in breast cancer patients with bone metastases held much promise for early diagnosis of skeletal metastases, estimation of severity, and monitoring the efficiency of bisphosphonate therapy [12].

Chao *et al*. determined TRAP in 30 early breast cancer patients without bone metastases, 30 aged-matched breast cancer patients with bone metastases, and 60 normal and

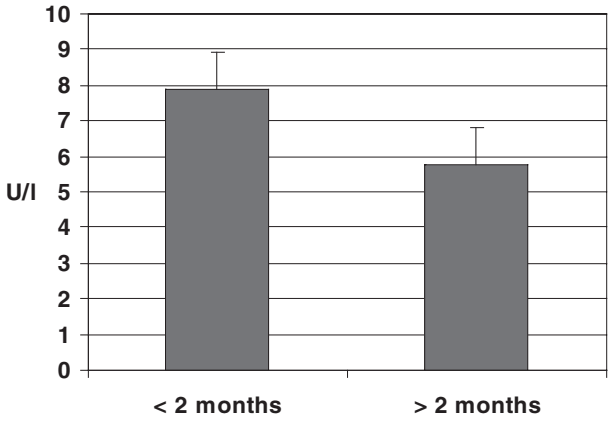


Figure 16. — BoneTRAP of all patients

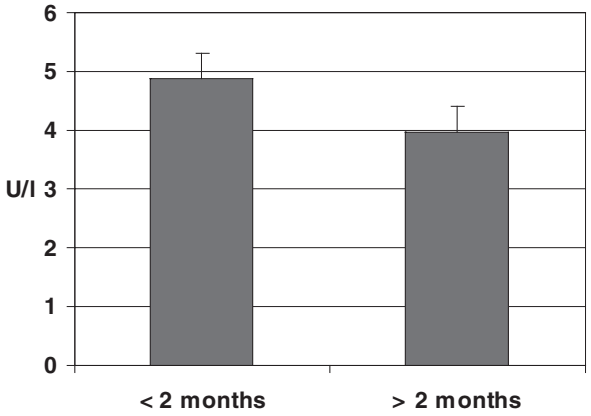


Figure 17. — BoneTRAP of patients < 3 locations.

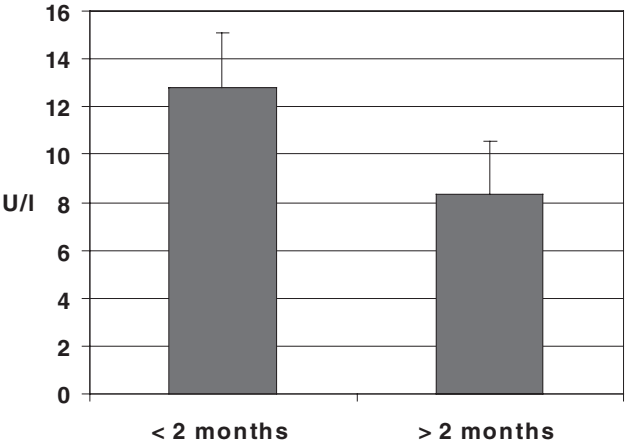


Figure 18. — BoneTRAP of patients > 3 locations (* $p < 0.05$)

healthy volunteers as controls [13]. The mean TRAP activity in early breast cancer patients did not differ significantly from that of the normal group whereas it was significantly higher in patients with bone metastases ($p < 0.0001$) [13].

We found no studies regarding oral therapy with clodronate in measuring TRAP as a marker. However there is experimental evidence that therapy with pamidronate could be monitored by the determination of TRAP.

Martinetti *et al*. treated 28 advanced breast cancer patients with bone metastases with the bisphosphonate of pamidronate using a total of 24 infusions over a treatment period of 61 weeks [14]. To evaluate the usefulness of TRAP in monitoring the treatment with pamidronate, patients were divided into two groups with respect to pain trend and analgetic intake. The results did not show any statistical significance in the baseline serum TRAP levels in the two groups. One week after the first pamidronate infusion TRAP serum levels decreased by 39% and 18% in group A and B. These levels persisted throughout the treatment period. They concluded that a decrease in TRAP serum levels may reflect the pharmacological activity of pamidronate [14].

Mose *et al*. monitored the effectiveness of local radiotherapy in 48 breast cancer patients with bone metastases by determination of the active isoform 5b of tartrate-resistant acid phosphatase [15]. They found a significant decrease of TRAP in patients without progression in non-irradiated regions, whereas in progressive disease TRAP remained stable with a slightly increasing tendency ($p < 0.01$). Like our study, Mose *et al*. showed that in patients with more than three locations of bone metastases all TRAP values were significantly higher compared to patients with less than four locations ($p = 0.01$) [15].

Our study demonstrated that patients with progressive bone metastases can benefit from therapy with clodronate much more than patients with only one or two locations. As our data show a period of clodronate therapy of at least two-months is necessary to significantly reduce the activity of TRAP.

Conclusion

The possible significance of TRAP includes its use as a screening parameter in the first staging of diagnosed breast cancer. It may be able to indicate one day if change to another bisphosphonate is useful in the therapy of a woman with bone metastases. It would be of immense value in evaluating the risk of a breast cancer patient developing bone metastases in order to start prophylactic therapy at once.

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