Procollagen Type 1 Amino-terminal Propeptide: A Marker for Bone Metastases in Prostate Carcinoma

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Abstract. *Background: The objective of this study was to assess the utility of the bone formation marker procollagen type I amino-terminal propeptide (P1NP) in indicating bone metastases in patients with prostate carcinoma. Alkaline phosphatase (AP) and prostate-specific antigen (PSA) were measured as a comparison. Patients and Methods: The serum samples of 100 patients were analysed using a specific immunoassay. The patients were divided into three groups, 32 patients with benign prostate hyperplasia (BPH), 38 patients with prostate carcinoma and 30 patients with prostate carcinoma with bone metastases. Results: P1NP concentrations were elevated in about 87% of the patients with confirmed bone metastases, the P1NP levels were significantly (p≤0.001) higher (median: 194.7 ng/ml) than in the patients without bone involvement (median: 38.0 ng/ml) and the BPH patients (median: 42.2 ng/ml), who both presented P1NP levels within the normal range. Conclusion: P1NP is a reliable predictor of the presence or absence of bone metastases in prostate carcinoma.*

With about 218,890 new cases and about 27,050 deaths in the United Stated in 2007, prostate carcinoma is the most frequent male cancer and the second leading cause of death from cancer among men (1). With an incidence of 65-75% , bone involvement, especially metastatic spread into the axial skeleton, is a major cause of morbidity and mortality in patients with prostate carcinoma (2). In order to provide appropriate treatment, the early detection of metastatic bone disease is an essential part of primary cancer staging and follow-up. Bone scintigraphy is the standard method currently applied to detect bone metastases, but despite its high sensitivity, this technique lacks specifitity as hot spots may also be due to trauma, infection and arthropathy (3, 4). The prostate-specific antigen (PSA) is another diagnostic modality for determining the presence or absence of bone metastases in patients with prostate carcinoma. In patients with PSA levels <10 ng/ml, the likelihood of abnormal bone scan results is less than 0.5% (5); in patients with PSA levels between 20 and 100 ng/ml, the likelihood is 50-60% (6). Recently, different circulating biochemical markers of osteoblastic and osteoclastic activity have turned out to be a useful, noninvasive and comparatively inexpensive method for the assessment and monitoring of metastatic bone involement (7). As bone metastases in prostate cancer are predominantly of an osteoblastic nature (8), markers of bone formation are of special interest. In addition to alkaline phosphatase (AP), which is already applied in clinical routine (9), the new marker procollagen type I amino-terminal propeptide (P1NP), a by-product of the synthesis of bone collagen, has gained clinical attention because of its accuracy in detecting metastatic bone disease in patients with breast cancer (10).

The aim of the present study was to examine whether P1NP might be an appropriate marker to discriminate between patients with and without bone metastases in prostate carcinoma.

Patients and Methods

Our unblinded study included 100 patients, who were treated in the Hospital of the Johann Wolfgang Goethe University, Frankfurt. For the purposes of this study, they were divided into three groups: the first group included 32 patients with benign prostate hyperplasia (BPH), the second contained 38 patients with histologically confirmed prostate carcinoma without bone metastases (TxBM (–)) and the third consisted of 30 patients with prostate carcinoma and bone involvement (TxBM (+)). Table I presents the demographic and clinical characteristics of the three study groups. For clinical staging, the patients were classified in accordance with the TNM staging system, using digital rectal examination, transrectal ultrasonography, biopsy and serum levels of the PSA. To determine the presence of bone metastases, bone scintigraphy was performed. Exclusion criteria were bone fractures near to the time of blood sampling and manifest osteoporosis. No patient was taking drugs known to affect bone metabolism.

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Table I. *Characteristics of the study groups.*

	BPH	TxBM (–)	TxBM (+)
No.	32	38	30
Mean age (years)	65.5	66.4	70.3
Tumor stage no.			
T1		9	2
T2		19	9
T3		9	8
T4		1	11

BPH: benign prostate hyperplasia; TxBM (–): prostate carcinoma without bone metastases; TxBM (+): prostate carcinoma with bone metastases.

To perform the P1NP measurements, blood samples were collected from the 100 patients with BPH and prostate carcinoma between January 2006 and July 2007. The sera were separated from the blood by centrifugation within 1 h after sample collection and then frozen and stored at –80˚C until P1NP analysis. The serum P1NP was measured with the electrochemiluminescence immunoassay ECLIA using an Elecsys 2010 analyzer (Roche Co., Mannheim, Germany). This method is based on a sandwich principle, using streptavidin-coated microparticles, biotinylated monoclonal anti-P1NP antibodies and monoclonal anti-P1NP antibodies labeled with a ruthenium complex. PSA and AP were also measured in order to compare their diagnostic effectiveness with P1NP.

The values are shown as median and range. Sensitivity, specificity and positive and negative predictive values were also calculated. Receiver operating characteristic curves (ROC) were analyzed in order to compare the power of differentiation of P1NP, PSA and AP between patients with and without bone metastases. All the statistical calculations were performed with SPSS® 11.0, SPSS Inc. 2001 and Microsoft® Office Excel 2003.

Results

In this study, the P1NP cut-off was 60 ng/ml, the PSA cut-off was 10 ng/ml and the AP cut-off was 129 U/l. Table II shows the results for each marker. The patients with BPH (median 42.2 ng/ml) and prostate carcinoma without bone metastases (median: 38.0 ng/ml) had P1NP levels within the normal range. Furthermore, the median P1NP concentration did not differ significantly (p=0.19=n.s.) between these two groups of patients without malignant changes in bone metabolism. In contrast, the patients with bone metastases had significantly ($p \leq 0.001$) higher P1NP concentrations (median: 194.7 ng/ml).

Similar results were observed for AP. In the BPH group (median: 68.0 U/l) and the TxBM (–) group (median: 66.0 U/l), the serum levels of this bone formation marker were significantly ($p \leq 0.001$) lower than in the TxBM (+) group (median: 144.0 U/l).

The patients with BPH (median: 4.4 ng/ml) had significantly ($p \leq 0.001$) lower PSA values than the patients in the TxBM (–) group (median: 9.2 ng/ml). The serum levels of the patients with metastatic spread into the skeletal system (median: 119.0 ng/ml) were elevated even beyond the median PSA concentration of the TxBM (–) group.

Table II. *Serum P1NP, PSA and AP in the three study groups.*

Study group	P1NP (ng/ml)		PSA (ng/ml)		AP (U/l)	
	Median	Range	Median	Range	Median	Range
BPH	42.2	11.3-132.3	4.4	0.50-68.4	68.0	46.0-184.0
Tx BM (–)	38.0	11.1-155.0	9.2	0.03-190.0	66.0	23.0-127.0
Tx BM (+)	194.7	19.6-1218.9	119.0	0.60-2390.0	144.0	36.8-718.0

Table III. *Comparison of P1NP, PSA and AP.*

	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
P1NP	86.7	78.0	63.4	93.2
PSA	90.0	51.9	64.3	93.8
AP	53.8	93.3	98.5	84.8

As illustrated in Table III, sensitivity, specificity, positive and negative predictive value were calculated for each parameter. Although the PSA level was about 3.3% more sensitive than the P1NP concentration in determining whether the prostate carcinoma had metastasized to the bone, P1NP was unequivocally the more specific marker. When compared with the AP, P1NP had a 33% higher sensitivity, although the specificity of AP exceeded that of P1NP.

ROC curves for each marker were calculated, revealing similar curves for P1NP and PSA. The areas under the curves (AUC) were 0.887 for P1NP, 0.911 for PSA and 0.796 for AP, respectively.

Discussion

With the aging of the population and the introduction of PSA as a screening parameter, an increasing incidence of prostate carcinoma has been observed (11) and over 20% of the newly diagnosed patients already have advanced or even metastatic disease. PSA is a sensitive marker for discriminating between benign and malignant processes in the prostate and is the tumour marker of choice for detecting and monitoring prostate carcinoma. In the present study, the patients with bone metastases showed significantly higher PSA concentrations than did the patients without bone involvement and sensitivity was high (90.0%). Nevertheless, Wymenga *et al.* found that in 13% of patients with bone metastases the wrong diagnosis was made if PSA levels were the only diagnostic criteria (12). Although increasing PSA levels are paralleled by disease progression during follow-up, PSA has a limited ability to discriminate local from metastatic disease (13). Accordingly,

PSA has a low specificity for bone metastases. In the present study, the specificity was 51.9%, while Rudoni *et al*. calculated only 36% (14). Additionally, PSA is only useful in untreated patients. Patients receiving concurrent hormonal treatment may develop undetected new bone metastases because their PSA values are artificially lowered (15).

As bone metastases are associated with an increase in bone metabolism, new techniques attempt to identify malignant bone turnover by means of special tumour markers. AP, often applied in clinical routine, comprises different isoenzymes, especially the bone- and the liver-specific forms, contributing equally to the total. Thus, a rise in AP is not specific for bone metastases and concurrent hepatobilary dysfunction has to be ruled out in patients with suspected bone involvement (16).

As it is a highly sensitive and specific marker for osteoblastic activity, the new bone formation marker P1NP, a precursor molecule of bone collagen, seems to be a good indicator of osteoblastic metastases in patients with prostate carcinoma. According to the present results, nearly 87% of the patients with bone metastases showed elevated P1NP levels, thus offering the possibility of a reliable diagnosis. Furthermore, the patients with prostate carcinoma without metastatic bone disease and healthy men with BPH presented P1NP levels within the normal range. In a study from De la Piedra *et al*., a P1NP sensitivity and specificity of 100% was reported (17). In the present study, the sensitivity was 86.7% and the specificity was 78.0%. This difference might be due to the fact that the patients of these authors were all untreated, whereas some patients in the present study were under treatment. Thus, further studies may be necessary to evaluate the influence of treatment on P1NP serum levels in patients with prostate carcinoma.

In the present study, the advantage of P1NP compared to PSA and AP became evident in the high diagnostic sensitivity as well as high specificity, whereas the other two markers either lacked sensitivity (AP) or specificity (PSA) with levels of just about 50%. Thus the bone formation marker P1NP, in contrast to PSA, significantly differentiated between the presence and absence of bone metastases, independent of local tumour progression. In comparison with the bone formation marker AP, P1NP should be preferred because it is not influenced by the development of visceral metastases.

Conclusion

The bone formation marker P1NP seems to be useful for assessing and managing patients with prostate carcinoma, as highly elevated P1NP concentrations are significantly associated with the presence of bone metastases.

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