ONCOLOGY

Tartrate-Resistant Acid Phosphatase as a Marker of Bone Metastases in Patients with Breast Cancer and Prostate Cancer

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Serum activity of tartrate-resistant acid phosphatase 5b (TRAP 5b) in patients with breast cancer and prostate cancer having bone metastases was much higher than in healthy donors and patients without skeletal injuries. TRAP 5b activity in patients with breast cancer and multiple bone metastases surpassed that in patients with single bone metastases. The mean activity of TRAP 5b and range of enzyme activity in women treated with bisphosphonates were significantly lower than in patients not receiving antiresorptive therapy. Diagnostic sensitivity and specificity of TRAP 5b as a marker of skeletal metastases in patients with breast cancer were 82 and 87%, respectively. In patients with prostate cancer these indexes were 71 and 83.4%, respectively. Detection of this marker in tumor patients holds much promise for early diagnostics of bone metastases, estimation of the severity of skeletal metastases, and monitoring of the efficiency of bisphosphonate therapy.

Key Words: *tartrate-resistant acid phosphatase; breast cancer; prostate cancer; bone metastases*

Breast cancer (BC) and prostate cancer (PC) are characterized by high osteotropism [1,2]. Early diagnostics of bone metastases is required for planning therapy, evaluation of the stage of the disease and its prognosis. However, modern instrumental methods for examination of the skeleton have low sensitivity and specificity [1,5]. Much recent attention is given to the development of noninvasive methods for the diagnostics of bone metastases using markers of bone remodeling. One of these markers is tartrate-resistant acid phosphatase 5b (TRAP 5b). TRAP 5b is synthesized only by osteoclasts and plays a role in bone resorption. The release of TRAP 5b into the blood is proportional to the intensity of bone resorption. Serum TRAP 5b activity does not depend on the functional state of the liver and kidneys, but reflects the intensity of bone resorption over the last 24 h [3,6,8].

Metastasizing of malignant breast tumors to bone tissue is accompanied by stimulation of osteolysis and increase in serum TRAP 5b activity. These changes are related to the release of TRAP 5b into the circulation [10]. The increase in TRAP 5b activity can result from bone PC metastases despite their osteoblastic nature [4]. Standardized methods for the detection of TRAP 5b were recently developed, but the data on the possibility of using this marker for the diagnosis of bone metastases are scanty and contradictory.

MATERIALS AND METHODS

We examined 48 patients with BC (30-74 years, 32 patients with bone metastases and 16 patients without

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TABLE 1. TRAP 5b Activity in the Serum from Patients with BC and PC (*M±m*)

Group		Number of patients	Age, years	TRAP 5b activity, U/liter
Control		13	60.0±2.2 (48-72)	2.70±0.23 (0.56-3.31)
BC patients	with bone metastases	32	52.0±2.1 (30-74)	8.7±1.0*+ (3.1-25.2)
	without bone metastases	16	56.00±4.27 (36-73)	3.87±0.45* (1.7-8.8)
PC patients	with bone metastases	14	62.8±2.0 (52-72)	7.84±1.37*+ (1.17-13.4)
	without bone metastases	6	65±3 (60-73)	2.56±0.30 (0.88-2.9)

Note. *$p<0.05$ compared to the control; +$p<0.001$ compared to patients without bone metastases.

clinical signs for skeletal injury) and 20 patients with PC (52-73 years, 14 patients with metastases and 6 patients without bone metastases). The control group included 13 healthy women and men (48-72 years).

TRAP activity was measured by enzyme immunoassay with monoclonal antibodies highly specific for the bone isoform of 5b (Bone TRAP Assay, Medac Diagnostika).

The results were analyzed by Student's *t* test. The differences were significant at $p<0.05$. Correlation analysis involved nonparametric Spearman test (*R*).

RESULTS

Serum TRAP 5b activity in BC and PC patients with skeletal injury was higher than in healthy donors by 3.0 and 2.9 times, respectively ($p<0.001$, Table 1). It should be emphasized that TRAP 5b activity in patients with BC was higher that in patients with PC. In practically all patients with BC, TRAP 5b activity surpassed the mean level observed in healthy donors.

TRAP 5b activity in BC and PC patients with bone metastases was much higher than in patients of the corresponding groups without skeletal injury ($p<0.001$, Table 1). Enzyme activity increased by 1.3 times in patients with BC not having clinical signs of skeletal injury ($p<0.05$). However, TRAP 5b activity in PC patients without bone metastases was similar to that in healthy donors.

Previous observations showed that TRAP 5b activity can increase in postmenopausal women due to high-intensity bone resorption [9,11]. We studied the dependence of enzyme activity on the age and menstrual function in patients with BC and bone metastases. No differences were found in mean activity of TRAP 5b and range of enzyme activity in patients of the reproductive age and postmenopausal women (Table 2). No correlation was revealed between TRAP 5b activity and age of patients (r=-0.006).

We evaluated the clinical significance of TRAP 5b as a marker of bone metastases.

Diagnostic sensitivity and specificity of TRAP 5b were estimated by the threshold value (4.3 U/liter). It was calculated from the mean and two standard deviations in healthy donors (95% confidence interval).

TRAP 5b activity in 26 of 32 patients with BC and bone metastases (82%) surpassed the threshold value. Serum TRAP 5b activity was measured in 16 BC patients without bone metastases to estimate diagnostic specificity of the enzyme. Our study yielded only two false-positive results, which corresponded to a specificity of 87%. TRAP 5b activity in 10 of 14 patients with PC and bone metastases (82%) surpassed the threshold value (diagnostic specificity 71%). Studying the serum from 6 patients with PC not having bone metastases produced only one false-positive result (diagnostic specificity 83%).

TABLE 2. Dependence of TRAP 5b Activity in Patients with BC and Bone Metastases on Menopause Status (*M±m*)

Group	Number of patients	Age, years	TRAP 5b activity, U/liter
Premenopausal patients	14	42.8±1.2 (30-50)	8.10±0.72 (3.1-23.9)
Postmenopausal patients	18	62.3±2.2 (51-74)	8.8±1.5 (3.7-25.2)

TABLE 3. Dependence of TRAP 5b Activity in Patients with BC and Bone Metastases on Bisphosphonate Therapy

Group	Number of patients	TRAP 5b activity, U/liter
Patients not receiving bisphosphonates	22	9.57±1.3 (3.7-25.2)
Patients receiving bisphosphonates	10	6.1±0.8* (3.1-10.2)

Note. *$p<0.02$ compared to patients not receiving bisphosphonates.

It should be noted that the data on diagnostic significance and specificity of TRAP 5b are preliminary, because of low number of examined patients. Further observations should be conducted on more representative groups of patients.

The study of the severity of skeletal injury is an urgent clinical problem. X-ray examination and scintigraphy were performed to evaluate the dependence of TRAP 5b activity on the degree of metastasizing. BC patients were divided into 2 groups. Group 1 included 8 patients with single bone metastases. Group 2 consisted of 24 patients with multiple skeletal injuries. Significant intergroup differences were revealed in TRAP 5b activity ($p<0.001$). The mean activity of serum TRAP 5b in patients with multiple bone metastases (10.2±1.3 U/liter) was 2-fold higher than in patients with single bone metastases (4.3±0.3 U/liter). Similarly to patients with multiple skeletal injuries, TRAP 5b activity in patients with single bone metastases was higher than in the control ($p<0.05$).

TRAP 5b activity can decrease during bisphosphonate therapy, which is related to suppression of osteoclast function [7,8]. The mean activity of TRAP 5b and the range of enzyme activity in patients with BC and bone metastases receiving bisphosphonates was much lower than in women not treated with bisphosphonates for a long time before examination (at least 6 months, Table 3).

Our results confirm high diagnostic sensitivity and specificity of TRAP 5b as a marker of bone metastases in patients with BC and PC. Detection of this marker in patients with malignant tumors holds much promise for the early diagnostics of bone metastases, estimation of the severity of bone metastases, and monitoring of the efficiency of bisphosphonate therapy.

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