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ORIGINAL ARTICLE

Prognostic role of serum cancer antigen 15-3 in breast cancer patients with isolated bone metastases

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Abstract

Objective: To investigate the association between cancer antigen (CA) 15-3 and clinicopathological parameters in patients who had breast cancer with isolated bone metastases at the time of diagnosis and to analyse the effect on clinical outcomes.

Methods: Between June 2004 and January 2007, the data of 129 consecutive patients were examined.

Results: Elevated CA 15-3 levels were associated with poor disease-free survival ($p = 0.001$) and overall survival ($p = 0.006$). In multivariate analysis, serum CA 15-3 level ($p = 0.003$) was found to be an independent factor in overall survival.

Conclusion: Elevated CA 15-3 level is a useful parameter for predicting clinical outcomes.

Keywords: *Breast cancer; bone metastasis; CA 15-3; prognosis; tumour marker*

Introduction

The potential uses of serum tumour markers in breast cancer include aiding early diagnosis, determining prognosis, prospectively predicting response or resistance to specific therapies, surveillance after primary surgery and monitoring therapy in patients with advanced disease (Duffy 2006). Metastatic breast cancer patients have a tumour load. It is difficult to quantify tumour load with imaging studies and some patients have evaluable but not measurable disease. Serum cancer antigen (CA) 15-3 levels are used as a marker of disease bulk in monitoring metastatic disease and for the preclinical detection of tumour recurrence (Ali et al. 2002). The American Society of Clinical Oncology (ASCO) guidelines address the value of this serum marker at detecting recurrence; there are no prospective randomized clinical trials to demonstrate whether detection and treatment of occult or asymptomatic metastases using tumour markers impact on the most significant outcomes (Harris et al. 2007).

In this study, we evaluated the ability of serum tumour markers in predicting metastatic breast cancer outcome and the relationship between the serum CA 15-3 levels and clinicopathological parameters.

Methods

Ethical consideration

The data were collected retrospectively and approved by our institutional ethical committee.

Study population

Between June 2004 and January 2007, the data of 129 consecutive female patients who were diagnosed as breast carcinoma with isolated bone metastases were identified. The inclusion criteria of the patients who were treated in Ankara Oncology Education and Research Hospital were patients with unilateral breast cancer and patients without concomitant cancer. Bone metastasis was diagnosed by imaging modalities. Histopathological bone examination was used only for patients who had pathological bone fractures. The bone metastases in 42

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patients (32.6%) were synchronous (the patients were found to have isolated bone metastases at the time of or within 6 months of breast cancer diagnosis) and in 87 patients (67.4%) were metachronous (bone metastases developed in the patients only after breast cancer surgery). A chemiluminescent enzyme immunoassay was used to measure serum CA 15-3 levels. All patients had routine measurement of serum CA 15-3 levels and measurements were repeated at the time of clinic visits. The cut-off limit was established at 30.0 U ml^{-1} which is the upper limit of normality. These patients were classified into two groups depending on the serum CA 15-3 levels at the bone metastasis development time. Group I (n = 48) and group II (n = 81) were defined according to tumour marker levels that were normal or elevated, respectively.

Compared parameters

Age, menopausal status, development time of bone metastasis (synchronous or metachronous), histological type, tumour size, grade, estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor 2 (HER-2/neu) receptor status, systemic treatment modalities received and the response to systemic treatments were compared in each group. The status of ER, PR and Her-2/neu proteins were examined by immunochemistry. ER and PR status were categorized as positive when ≥10% of tumour cells expressed ER or PR. HER-2/neu protein expression was evaluated on staining pattern (0, +, 2+, and 3+) and HER-2/neu 2+ was considered positive if fluorescence *in situ* hybridization or silver-enhanced *in situ* hybridization was positive. The effects of serum Ca 15-3 levels and other effective parameters on time to progression and overall survival were investigated.

Systemic treatment

Systemic hormonal and/or cytotoxic therapy was given to the patients after the diagnosis of isolated bone metastases. Hormonal therapy only was used in 73 patients. Tamoxifen for the premenopausal patients and tamoxifen or aromatase inhibitors for the postmenopausal patients were preferred. Chemotherapy only was used in 19 patients. The remaining 37 patients received chemotherapy and hormonal therapy. First-line, anthracycline-containing regimens were preferred. The FAC regimen (5-fluorouracil 600 mg m^{-2} intravenously (i.v.) day 1, doxorubicin 60 mg m^{-2} i.v. day 1, cyclophosphamide 600 mg m^{-2} i.v. day 1, and every 3 weeks for six cycles) was used in 25 patients who received chemotherapy. Four patients received the TAC regimen (docetaxel 75 mg m^{-2} i.v. day 1, doxorubicin 60 mg m^{-2} i.v. day 1, cyclophosphamide 600 mg m^{-2} i.v. day 1, and every 3 weeks for six cycles) and the remaining patients received four cycles of FAC and four cycles of the TAC regimen. Trastuzumab was used for the patients whose Her-2/neu gene amplification was positive. Also, 76.3% of patients were given zoledronate 4 mg intravenously monthly and 23.7% of patients were given 1600 mg oral clodronate daily. Twenty-four patients required palliative radiotherapy at some time during the course of their disease

Follow-up procedure

Follow-up for all patients included history taking, a physical examination of the breast and axilla, and laboratory tests, including CA 15-3, liver function tests, full blood count at 3–6 month intervals, and annual bone scan and mammography with ultrasound. Other imaging studies were done only on the basis of symptoms or physical findings.

Disease progression

The appearance of new lesions on imaging studies, > 30% increase in serum CA 15-3, and/or alkaline phosphates levels that lasted for > 2 months (in osteolytic metastases), and the progression of disease-related symptoms were considered as symptoms of progressive disease. If there was disease progression especially in the first 6 months, it was considered as a failure to respond to systemic treatment.

Statistical analyses

The χ^2 test or the Fisher's exact test was used to compare the distribution of patient demographic characteristics and tumour-related characteristics between the groups. Univariate survival curves for disease-free survival and death were estimated by using the Kaplan–Meier method; group differences in survival time were tested by the log-rank test. Multivariate Cox regression analysis was carried out to compare and identify independent prognostic factors for disease-free survival and death and to calculate risk ratios. All significant parameters in univariate analyses were entered into a multivariate model and excluded for p-value >0.05. SPSS for Windows (version 13.0) was used for all statistical analyses.

Results

Serum CA 15-3 levels were elevated in 62.8% of patients when isolated bone metastases were diagnosed. When the data collection was completed in July 2009, the patients had a median follow-up of 38 months (range 8–105) after the diagnosis of bone metastases. The groups and the comparison results are shown in Table 1. The two

groups were similar when patients' tumour characteristics and systemic treatment modalities were compared. The effectiveness of chemotherapy between the groups after developing bone metastases was analysed. In the first 6 months, there was chemotherapy resistance in 10 out of 48 patients in group I and 27 out of 81 patients in group II which was not found to be statistically significant ($p = 0.54$).

The patients who had normal and elevated serum Ca 15-3 levels were compared for time to progression and overall survival. The survey graphics are given in Figures 1 and 2. Clinical progression was observed in 40 out of 48 patients (83.3%) in group I and 79 out of 81 patients (97.5%) in group II during follow-up time. Localization of progressive disease was compared, and the outcomes are given in Table 2. Although, the visceral progression was disproportionately more frequent in the elevated CA 15-3 group compared with the normal CA 15-3 group, the difference was not significant ($p = 0.14$).

The age, menopausal status, development time of bone metastasis, histological type, tumour size, grade, ER, PR and Her-2/neu receptors, and serum CA 15-3 levels were examined as the factors that affected the overall survival and time to progression of the patients. Serum CA 15-3 level ($p = 0.001$, relative risk (RR) 2.00, 95% confidence interval (CI) 1.35–2.96) was the only parameter which affected time to progression. For overall survival, related risk factors based on the univariate analysis are given Table 3. In multivariate analysis, the serum CA 15-3 level ($p = 0.003$, RR 2.51, 95% CI 1.36–4.64) was found to be an independent factor associated with overall survival. At the end of the study period, 34 patients (70.8%) in group I and 33 patients in group II (40.7%) were still alive. The death ratio ($p = 0.001$, RR 1.57, 95% CI 1.19–2.07) was high in the second group.

Discussion

Tumour markers, such as CA 15-3 and carcinoembryonic antigen have been evaluated as predictive parameters in patients' outcome and treatment response.

Table 1. Comparison criteria between the groups of breast cancer patients with isolated bone metastasis.

		Normal CA 15-3 levels Group I ($n = 48$)	Elevated CA 15-3 levels Group II ($n = 81$)	p-Value
Age of metastatic patients (years), mean		52 ± 14	51 ± 12	0.82
Menopausal status	Pre	21 (43.8)	31 (38.3)	0.54
	Post	27 (56.2)	50 (61.7)	
Development time of bone metastases	Synchronous	15 (31.2)	27 (33.3)	0.80
	Metachronous	33 (68.8)	54 (66.7)	
Histological type	IDC	44 (91.6)	67 (82.7)	0.32
	ILC	3 (6.3)	12 (14.8)	
	(IDC+ILC)	1 (2.1)	2 (2.5)	
Tumour size	T1–2	27 (56.3)	40 (49.4)	0.58
	T3–4	20 (41.6)	37 (45.7)	
	Tx	1 (2.1)	4 (4.9)	
Bloom–Richardson grade	Grade 1	_	_	0.54
	Grade 2	28 (58.3)	46 (56.8)	
	Grade 3	18 (37.5)	30 (37.0)	
	(Unknown)	2 (4.2)	5 (6.2)	
ER status	(-)	8 (16.7)	14 (17.3)	0.74
	(+)	36 (75.0)	63 (77.8)	
	(Unknown)	4 (8.3)	4 (4.9)	
PR status	(-)	14 (29.2)	24 (29.6)	0.83
	(+)	25 (52.1)	45 (55.6)	
	(Unknown)	9 (18.7)	12 (14.8)	
cerbB2/neu	(-)	24 (50.0)	48 (59.3)	0.98
	(+)	9 (18.7)	18 (22.2)	
	Unknown	15 (31.3)	15 (18.5)	
Systemic treatment	HT	31 (64.6)	42 (51.9)	0.19
	CT	4 (8.3)	15 (18.5)	
	CT+HT	13 (27.1)	24 (29.6)	

IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; ER, estrogen receptor; PR, progesterone receptor; HT, hormonotherapy; CT, chemotherapy.
Values are *n* (%) unless otherwise indicated.

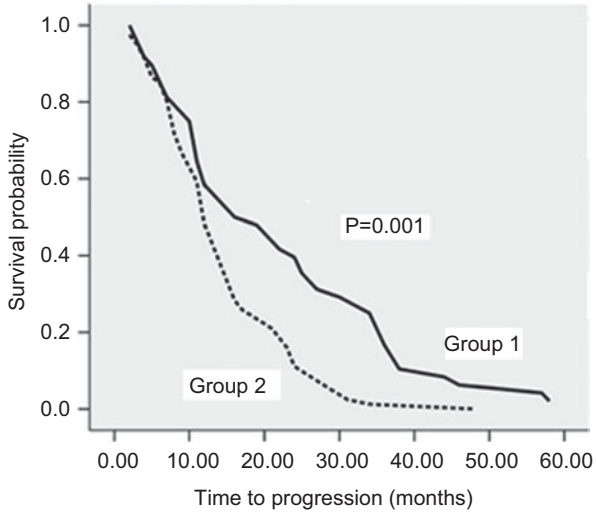

Figure 1. The effect of serum Ca 15-3 levels on time to progression (Kaplan–Meier curve) after bone metastasis.

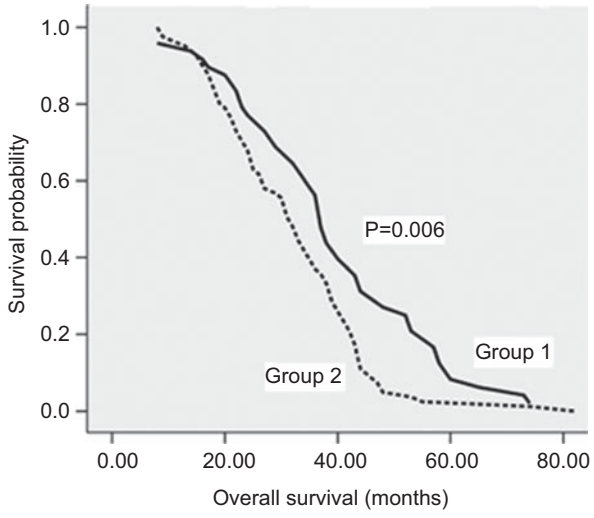

Figure 2. The effect of serum CA 15-3 levels on overall survival (Kaplan–Meier curve) after bone metastasis.

Table 2. First progression area after bone metastasis.

	Normal CA 15-3 levelsGroup I ($n = 48$)	Elevated CA 15-3 levelsGroup II ($n = 81$)	p-Value
Bone	25	40	0.14
Local	3	4	
Visceral	7	20	
Local and visceral	2	2	
Bone and visceral	3	13	

The sensitivity of these markers is low, so that they are not useful screening tools (Harris et al. 2007). In addition, tumour marker levels tend to increase as tumour progression occurs; therefore, it has limited diagnostic

Table 3. Overall survival: related risk factors based on the univariate analysis.

	n	%	p-Value
Age of metastatic patients, mean 51.5 ± 12.7 years	129	100	0.001
Menopausal status			
Pre	52	40.3	0.03
Post	77	59.7	
Serum CA 15-3 levels			
Normal	48	37.2	0.006
High	81	62.8	
Development time of bone metastases			
Synchronous	42	32.6	0.17
Metachronous	87	67.4	
Histological type			
IDC	11	85.9	
ILC	11	11.7	0.69
(IDC+ILC)	53	2.4	
Tumour size			
T1–2	67	51.9	0.37
T3–4	57	44.2	
Tx	5	3.9	
Bloom–Richardson grade			
Grade 2	74	57.4	
Grade 3	48	37.2	0.66
(Unknown)	7	5.4	
ER status			
(-)	22	17.1	
(+)	99	76.7	0.70
(Unknown)	8	6.2	
PR status			
(-)	38	29.5	
(+)	70	54.3	0.16
(Unknown)	21	16.2	
cerbB2/neu			
(-)	72	55.8	
(+)	27	20.9	0.37
Unknown	30	23.3	

IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; ER, estrogen receptor; PR, progesterone receptor.

use. In 2007, the American Society of Clinical Oncology guidelines recommended that the serum CA 15-3 levels contributed to therapy for metastatic breast cancer. Present data are insufficient to recommend the use of CA 15-3 alone for monitoring the treatment response. CA 15-3 can be used in conjunction with diagnostic imaging, history and physical examination. However, the guidelines also stated that in exceptional circumstances, such as the presence of bone metastasis, which are difficult to evaluate clinically, the marker levels may be able to support the clinical influence of the disease status (Duffy 2006, Harris et al. 2007). In contrast to the ASCO panel, both the National

Academy of Clinical Biochemistry and the European Group on Tumor Markers Panels recommended the use of CA 15-3 for monitoring therapy in patients with advanced breast cancer (Molina et al. 2005, Fleisher et al. 2002).

While a number of previously published studies have shown that CA 15-3 is an adverse prognostic marker in breast cancer, this study shows this to be the case at the time isolated bone metastasis is first detected. Several studies demonstrated that circulating markers have prognostic relevance in early-stage breast cancer (Park et al. 2008, Uehara et al. 2008, Kumpulainen et al. 2002, Ebeling et al. 2002, Gion et al. 2002). In one of the studies, which included 1046 patients, Ebeling et al. (2002) reported CA 15-3 to be a predictor of worse outcome in univariate but not multivariate analysis, including tumour size, lymph node status, histological grade and ER status. Park et al. (2008) studied 740 patients with tumour stage I–III and defined that elevated CA 15-3 values were associated with poor disease-free survival and also with overall survival. However, in tumour stage-matched analysis, elevated CA 15-3 levels showed significantly poorer disease-free survival and marginally poorer overall survival in stage III. In another study including 1465 operable breast cancer patients by Uehara et al. (2008), the serum CA 15-3 levels had significance in prognosis only in stage II disease. A single study mentions that CA 15-3 levels do not have prognostic value in patients with negative axillary nodal metastases (Molina et al. 2003).

CA 15-3 levels are predictive for response and disease recurrence in following treatment of locally advanced breast cancer (Al-azari et al. 2006). Elevated CA 15-3 level is predictive for a poor response to chemotherapy but this study did not demonstrate an association between the tumour marker levels and systemic treatment response.

The importance of CA 15-3 in metastatic breast cancer has been studied prospectively (Tampellini et al. 1997). In univariate analysis, low CA 15-3 together with the absence of visceral metastasis and presence of only one metastatic site had a positive prognostic influence. In the Cox proportional hazard analysis, CA 15-3 was not an effective parameter in survival. This study reveals that if high levels of CA 15-3 are determined at the time of bone metastasis in breast cancer patients then the disease has a poor prognosis. However, it was shown that the use of an intensive follow-up programme or monitoring the marker levels failed to improve survival (GIVIO 1994, Rosselli del Turco et al. 1994, Rojas et al. 2005).

This study is important because of the applied uniform treatment of patients by a single institute as well as the study period comprising past years. In addition, this study consists of only bone metastatic patients. Bone-only disease is hard to follow clinically because of the non-measurable disease and the use of CA 15.3 in combination with it can be beneficial. The limitation of this study may be the high percentage of the patients (23.3%) who had unknown Her2/neu receptor status.

In conclusion, the present data show that elevated serum CA 15-3, determined when isolated bone metastasis is first detected in women with breast cancer, serves as a marker of poor prognosis of time to further progression of disease and of overall survival

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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