ORIGINAL ARTICLES

THE USE OF CA15-3 AND ESTROGEN RECEPTOR IN BREAST CANCER PATIENTS WITH BONE METASTASES

Tarkan KARAKAN, M.D., Nazan GÜNEL*, M.D., Zafer AKÇALI*, M.D., Aytuğ ÜNER*, M.D.

Gazi University, Faculty of Medicine, Departments of Internal Medicine and Medical Oncology*, Ankara, Turkey
Gazi Medical Journal 1998; 9 : 149-153

SUMMARY :

Purpose : *Skeletal metastasis of breast cancer has a better prognosis than visceral and soft tissue metastasis. Follow-up periods are relatively long and some clinical obstacles may occur in the assessment of bone metastasis. Biologic tumor markers are commonly used in the management of these cases. CA15-3 has recently been accepted as the most sensitive and specific tumor marker in breast cancer patients. Estrogen receptor (ER) status also plays role in the prognosis. In our study, we investigated the clinical usefulness of CA15-3 and ER status in metastatic breast cancer patients with bone metastasis.* ***Methods:*** *Our study group consisted of 108 breast cancer patients. Sixty-six (61.1%) of them had bone metastasis. CA15-3 levels, estrogen receptor status, disease free survival, overall survival, and metastatic patterns were evaluated. Statistical analyses were performed with chi-square test or Kaplan - Meier survival analysis.* ***Results:*** *We found that ER status is a favourable prognostic factor in breast cancer, which is compatible with the literature. Overall survival (OS) was improved for patients with bone metastasis compared with patients with other metastatic sites. An increased frequency of ER-positive patients was observed in bone metastatic group. There was significant correlation between high levels of CA15-3 and bone metastasis as the first metastatic site, but there was no relationship between CA15-3 and OS or ER status. The disease extent of bone metastatic patients had positive correlation with CA15-3, but there was a negative correlation between OS and disease extent.* ***Conclusion:*** *Although ER status is an important prognostic parameter, the clinical use of CA15-3 is especially valuable in the assessment of disease extent for bone metastasis. However, the predictive value of CA15-3 for prognosis is controversial.*

Key Words: *Breast Neoplasms, Tumor Markers, CA15-3 Antigen, Estrogen Receptors.*

INTRODUCTION

Despite developed techniques for detecting a tumor mass, the need exists for more practical, cheaper and sensitive laboratory methods that can indicate an occult cancer and the response to treatment. CA15-3, the most commonly used circulating tumor marker in breast cancer, is an antigen detected by its reaction with monoclonal antibodies 115D8 and DF3. The clinical usefulness of CA15-3 in evaluating response to treatment and recurrences has been widely studied. There are still some problems with these biological markers regarding low levels, lack of synthesis, lack of transfer to the systemic circulation, the effect of surgery, and the effect of chemotherapy (1).

Circulating tumor marker levels in advanced breast cancer correlate with the extent of metastatic disease. When CA15-3 was compared with another tumor marker CEA, the sensitivity and correlation with the extent the disease were higher for CA15-3 (2). Nevertheless, the role of CA15-3 in detection of early recurrences or its correlation with the prognosis and overall survival (OS) is still unclear. In this study, we investigated the clinical usefulness of CA15-3 and ER in metastatic breast cancer patients.

MATERIAL AND METHODS

We retrospectively reviewed the medical records of 108 patients with metastatic breast cancer treated in the Medical Oncology division at Gazi University Faculty of Medicine between 1993-1997. Of these 108 patients, 66 patients (61.1 %) had bone metastasis with or without non-skeletal metastasis. Bone metastasis were detected by bone scans and conventional X-ray methods. When necessary, computed tomography and magnetic resonance imaging were added in some cases. In this study; age, CA15-3 levels, estrogen receptor (ER) status, disease-free survival (DFS), overall survival (OS) and metastatic patterns of the patients were evaluated. Statistical analyses were performed with chi-square and Kaplan-Meier survival analysis, log-rank tests using SPSS 7.5 for Windows software package program. From the records, CA15-3 levels were available in 97 patients (90 %) and ER status in 49 patients (45 %). Both CA15-3 levels and ER status were available in 44 (40 %) patients. ER assay was evaluated by nuclear immunohistochemical staining of tumor cells at high power. CA15-3 determination was done with chemiluminescent enzyme immunoassay method using the Immulite 1000 automated analysis system (DPC). Serum samples were studied immediately and the results were given as U/ml. The upper range of CA15-3 cut-off value was determined as 60 U/ml. The Immulite automated immunoassay method read CA15-3 values between 0 – 300 U/ml. Chi-square test or Kaplan - Meier survival analysis was used for statistical evaluations.

RESULTS

In this study, median age was 50 (25-85) years at the time of first diagnosis. The median DFS was 15 (0-120) months (Table 1). CA15-3 and ER status of the patients as to their first metastatic site are shown in Table 2. The mean values of CA15-3 levels and ER positive status were significantly higher in patients with bone metastasis (Table 2). We could not find any significant difference between the CA15-3 high and normal groups (according to

Table 1: Patient characteristics.

Characteristics	
Age (years)	
Median	50
Range	25-85
DFS (months)	
Median	15
Range	0-120
OS (months)	
Median	36
Range	7-159
First metastatic site	
Bone (%)	66 (61)
Soft tissue and/or visceral (%)	42 (39)

DFS : disease free survival, OS : overall survival.

Table 2 : CA15-3 and ER status according to the first metastatic site

Markers	Bone	Soft tissue and/or visceral	
CA15-3			
Mean (U/ml±SE)	131.19±2.23	84.81±2.68	
High (%)	34 (35)	10 (10)	p<0.05
Normal(%)	24 (25)	29 (30)	
ER			
Positive(%)	28 (59)	9 (19)	p<0.05
Negative(%)	4 (8)	6 (14)	

Table 3 : Comparison of the ER status and the CA15-3 levels.

CA15-3 levels	High		Normal		
	n	%	n	%	
ER (+)	10	23	6	14	
ER (-)	10	23	18	40	p<0.086

Table 4 : Disease extent versus CA15-3 levels (bone metastasis group).

Disease extent	CA15-3 (high level)	CA15-3 (normal level)	
1*	4	9	
2+3**	21	11	p<0.05

*1= minimal, **2+3= moderate+extensive disease.

the ER status of the patients), (Table 3). Forty-four (45 %) patients with high CA15-3 levels and fifty-three (55 %) with normal CA15-3 levels had median OS as 53 and 41 months, respectively. There was no significant difference between these two groups. DFS of the patients was also evaluated. Forty-four (45 %) patients with high CA15-3 levels and 53 (55 %) with normal levels had median DFS as 29 and 18 months, respectively (p=0.041). When we consider patients with bone metastasis only, there was a trend of longer DFS in patients with high CA15-3 levels with no clear statistical significance (Fig. 1, p=0.05).

OS was evaluated without considering CA15-3 and ER status; a trend of longer survival is noted in patients with metastases confined to the skeletal system (Fig. 2, p=0.06). DFS did not correlate significantly with CA15-3 values in the same group. Disease extents of the patients with bone metastasis were estimated with modified Swenerton method (3). Minimal involvement (1-2 lesions on radiographs or bone scan) was 1, moderate (3-5 lesions) was 2 and extensive (>5 lesions) was 3. A correlation was found between the disease extent and CA15-3 values (p<0.05, Table 4 and Fig.3) or OS (p<0.05, Fig.4)

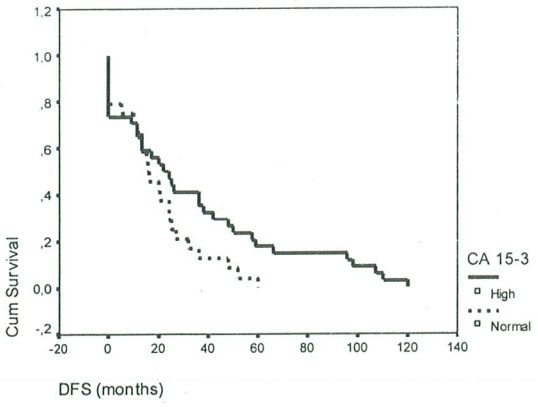

Fig - 1 : CA15-3 and DFS in bone metastasis.

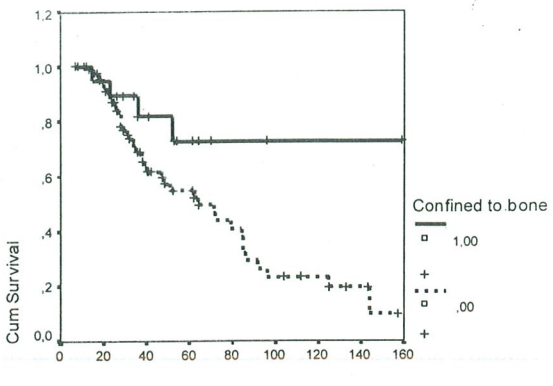

Fig - 2 : OS in metastatic breast cancer.

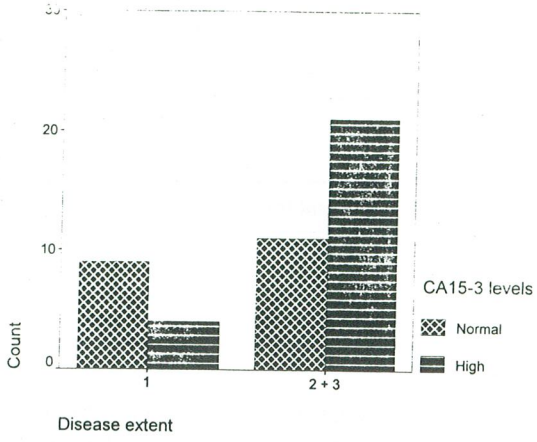

Fig - 3 : CA15-3 and disease extent in bone metastases.

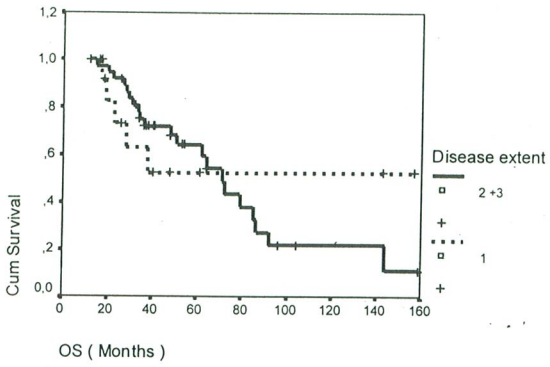

Fig - 4 : OS and disease extent in bone metastatic patients.

DISCUSSION

Metastatic breast cancer is an incurable disease, but metastasis of the breast cancer confined to the skeletal system is a distinctive subgroup of patients with longer survival rates and follow-up periods (3, 4). For this reason, objective measurements of response in palliative treatment and predicting outcome in various subgroups of these patients are valuable. ER activity of the primary tumor has a significantly favourable effect on the prognosis (5). Recent reports have conflicting data about the relationship between the ER status and the pattern of first metastasis. Some authors have found no difference in metastatic patterns related to the receptor status, but some claimed that a correlation exists between the ER status and the pattern of the metastasis (5). Patients with ER-positive tumors had bone metastases at first relapse three times more often than patients with ER-negative tumors; ER-negative tumors had visceral metastases more frequently (5). This different pattern of metastasis might have a correlation with the favourable prognosis in ER-positive tumors. Another study revealed correlation of PR (progesterone receptor) -positive status with higher CA15-3 levels (6). In our study, there is a correlation between bone metastasis and ER positive status (Table 2). EORTC (The European Organisation for Research and Treatment of Cancer) recommendations are mostly preferable for objective determination of ER status (7). In our series, ER status was determined by immunohistochemical staining of the nucleus in a high magnification area of the specimen. For this reason, ER determination method used in this study could have some effect on the results. CA15-3 has superior sensitivity compared with CEA and it is shown to be a preferable marker in the follow-up of patients with advanced disease (8). Although CA15-3 is widely used as a tumor marker in detecting distant metastases and response to treatment, its value in predicting the prognosis, disease-free and OS is a question of debate (9). In a prospective analysis of breast cancer cases with distant metastases, CA15-3 levels were found to be a dependent variable in determining survival, and its prognostic role was linked to the disease extent (2). Also, it has been shown that patients with elevated levels of CA15-3 in the postoperative period have a worse prognosis (8). Since higher levels reflect more advanced stages, elevated CA15-3 levels might only indicate micrometastases instead of biologic behaviour of the tumor. This association suggests that CA15-3 may be useful in assessing disease extent when tumor volume is not easily measurable (10). Another study concerning the prognostic value of CA15-3 and CA-125 indicated that both markers are independent prognostic factors in predicting OS at first relapse (11). Tumor marker sensitivity is also related to the site of recurrence, with the lowest sensitivity for locoregional relapse and highest for liver metastases, but, CA15-3 has no prognostic value in visceral metastases (9). In our study, the disease extent of patients with bone metastases correlated significantly with high CA15-3 levels

(Table 4 and Fig. 3), and there were higher CA15-3 levels for increased disease extent (Fig. 3) and a longer survival in patients with limited disease extent (Fig. 4). We found that patients with bone metastases had longer OS than the patients with non-skeletal metastases, which is compatible with the literature (Fig. 2). Although statistically non-significant, bone metastatic patients with high CA15-3 levels had a trend to longer DFS (Fig. 1). We could not find any evidence supporting this finding in the literature and further detailed studies may clarify this situation. As a result, CA15-3 is a useful marker in assessing the disease extent, but its role in predicting overall and disease free survival is not clear yet. The relationship between CA15-3 levels and ER status may be another topic of research. Although we found a statistically significant correlation between the disease extent and CA15-3 levels, larger studies are needed to make further comments.

Correspondence to : Dr.Nazan GÜNEL
Gazi Üniversitesi Tıp Fakültesi
Medikal Onkoloji Bilim Dalı
Beşevler
06500 ANKARA - TÜRKİYE
Phone : 312 - 214 10 00 / 5829

REFERENCES

1. Waalkes T P, Enterline J P, Shaper J H, Abeloff M D, Ettinger D S : Biologic Markers for breast carcinoma. Cancer 1984; 53 : 644-651.
2. Colomer R, Ruibal A, Salvador L : Circulating tumor marker levels in advanced breast carcinoma correlate with the extent of metastatic disease. Cancer 1989; 64 : 1674-1681.
3. Sherry M M, Greco F A, Johnson D H : Metastatic breast cancer confined to skeletal system. Am J Med 1986; 81 : 381-386.
4. Harris J R, Morrow M, Bonadonna G: Cancer of the breast. In. De Vita V T, Hellman Jr S, Rosenberg S A (ed) : Cancer Principles and Practice of Oncology. 4th ed. : Philadelphia J.B. Lippincott, 1993 :1264-1315.
5. Koenders PG, Beex LVAM, Langers R, Kloppenborg PWC, Smals AGH, Benraad Th J. Steroid hormone receptor activity of primary human breast cancer and pattern of first metastasis. The breast cancer study group. Breast Cancer Res Treat 1991; 18 : 27-32.
6. Molina R, Jo J, Zanon G, Filella X, Farrus B, Munoz M, Latre ML, Pahisa J, Velasco M, Fernandez P, Estape J, Ballesta AM : Utility of C-erbB-2 in tissue and in serum in the early diagnosis of recurrence in breast cancer patients : comparison with carcinoembryonic antigen and CA15-3. Br J Cancer 1996; 74 : 1126-1131.
7. E.O.R.T.C. Breast Co-operative Group. Revision of the standards for the assessment of hormone receptors in human breast cancer ; Report of the second E.O.R.T.C. Workshop, held on 16-17 March, 1979., in the Netherlands Cancer Institute. Eur J Cancer 1980; 16 : 1513-1515.
8. Hayes DF : Serum (circulating) tumor markers for breast cancer. In. Perry MC (ed) American Society of Clinical Oncology (ASCO) Educational Book. Thirty-third Annual Meeting.May 17-20, 1997 : 228-233.
9. Bomberdieri E, Pizzichetta M, Veronesi P, Seregni E, Bogni A, Maffioli L, Jotti GS, Bassetto M A, Zurrida S, Costa A : CA15-3 determination in patients with breast cancer : Clinical utility for the detection of distant metastases. Eur J Cancer 1993; 29A : 144-146.
10. Tampellini M, Berruti A, Gerbino A, Buniva T, Torta M, Gorzegno G, Ffaggiuolo R, Farris A, Destefanis M, Moro G, Deltotto F, Dogliotti L : Relationship between CA15-3 serum levels and disease extent in predicting overall survival of breast cancer patients with newly diagnosed metastatic disease. Br J Cancer 1997; 75 : 698-702.
11. Berruti A, Tampellini M, Torta M, Buniva T, Gorzegno G, Dogliotti L : Prognostic value in predicting overall survival of two mucinous markers: CA15-3 and CA125 in breast cancer patients at first relapse of disease. Eur J Cancer 1994; 30A : 2082-2084.