The potential role of preoperative serum cancer antigen CA 15-3 in the prognosis of breast cancer

Adela Stoenescu[2], Daniel Herr[1], Christoph Gerlinger[1], Erich Franz Solomayer[1], Christoph Scholz[2], Ingolf Juhasz-Böss[1], Julia Radosa[1]

[1] Department of Obstetrics and Gynaecology, University of Saarland, Homburg / Saar, Germany
[2] Department of Obstetrics and Gynaecology, University of Ulm, Ulm, Germany

ABSTRACT

Background: Serum CA 15-3 has been the most frequently investigated tumor marker in breast cancer. The most important application for CA 15-3 is in monitoring therapy in patients with advanced breast cancer. CA 15-3 levels have also been demonstrated to predict outcome in breast cancer. However, the potential role of CA 15-3 as a prognostic marker for breast cancer was investigated only in a few studies.

Methods: In a retrospective study, we investigated the association of the serum levels of CA 15-3 with tumor characteristics as prognostic factors of the disease. 586 female breast cancer patients confirmed by histopathological reports were included in the study. Information concerning age, menopausal status, diagnosis, and clinical pathology were collected for each patient. CA 15-3 serum levels were evaluated at time of the primary diagnosis.

Results: Our results suggest that elevated pretreatment serum marker values were correlated with poor prognosis and death from the disease. By comparing CA 15-3 levels in metastatic and non-metastatic disease, we found a statistically significant difference between the two categories. This study demonstrates a correlation between stage of breast cancer and CA 15-3 positivity rates. The higher the breast cancer stage, the more likely the CA 15-3 level will be elevated. The CA 15-3 level was similarly significantly related to death from disease. We found no correlation between CA 15-3 levels and recurrences of the disease.

Conclusion: Elevated preoperative serum level of CA 15-3 is significantly correlated with the presence of distant metastatic disease. Our data supports CA 15-3 as a useful parameter in the management of breast cancer preoperatively as well as in an adjuvant setting.

Keywords: Antigen CA 15-3, Breast cancer.

SOMMARIO

Background: Il CA 15-3 sierico è il marcatore tumorale più frequentemente studiato nel cancro al seno. L'applicazione più importante per il CA 15-3 è nel monitoraggio in pazienti con carcinoma mammario avanzato. E' stato dimostrato che Livelli di CA 15-3 sono in grado di predire l'esito del cancro al seno. Tuttavia, il ruolo potenziale di CA 15-3 come marcatore prognostico per il tumore al seno è stato valutato solo in pochi studi.

Metodi: In uno studio retrospettivo, abbiamo valutato l'associazione tra i livelli sierici di CA 15-3 e le caratteristiche del tumore come fattori prognostici della malattia. 586 pazienti con carcinoma mammario confermato da rapporti istopatologici sono state incluse nello studio. Informazioni riguardanti età, stato menopausale, la diagnosi e patologia clinica sono stati raccolti per ogni paziente. I livelli sierici di CA 15-3 sono stati valutati al momento della prima diagnosi.

Risultati: I nostri risultati suggeriscono che i valori elevati dei marker sierici pre-trattamento sono correlati con prognosi infausta e la morte per malattia. Confrontando i livelli di CA 15-3 in casi di malattia metastatica e non metastatica, abbiamo riscontrato una differenza statisticamente significativa tra le due categorie. Questo studio dimostra una correlazione tra lo stadio del cancro al seno e i livelli di CA 15-3.

Più avanzato è lo stadio del cancro al seno, più è probabile che il livello di CA 15-3 sia elevato. Il livelli di CA 15-3 sono stati correlati in maniera analoga e significativa alla morte per malattia. Non abbiamo riscontrato alcuna correlazione tra i livelli di CA 15-3 e le ricorrenze della malattia.

Conclusioni: Elevati livelli sierici pre-operatori di CA 15-3 sono significativamente correlati con la presenza di metastasi a distanza. I nostri dati supportano il CA 15-3 come parametro utile nella gestione preoperatoria del cancro al seno così come nella scelta della terapia adiuvante.

INTRODUCTION

Breast cancer is the most common cancer in women worldwide[18]. Nearly 1.1 million patients are diagnosed with breast cancer yearly[17]. The number of cases worldwide has significantly increased in the last years. New strategies for managing breast cancer are needed.

CA 15-3 is a high-molecular-weight mucin glycoprotein and is the most widely used serum marker in breast cancer for follow-up care and monitoring the treatment of patients with advanced disease[5,6]. For monitoring the treatment of advanced breast cancer, CA 15-3 levels decrease in approximately 70 % of patients with chemotherapy-induced breast cancer regression and increase in 80 % of patients with progressive disease[19].

Because of its low sensitivity (15-35 %), the routine use of CA 15-3 as a screening or diagnostic tool for primary breast cancer is not recommended[1-4]. Elevated levels of CA 15-3 are found in only 3 % of patients with non-metastatic breast cancer and in up to 70 % of patients with metastatic disease[16]. Increasing and decreasing levels show correlation with breast cancer progression and regression, respectively.

Nonmammary malignancies in which elevated CA 15-3 levels have been reported include: lung, colon, pancreas, primary liver, ovary, cervix, and endometrium. Mild increased concentrations were observed in benign conditions, such as:

hepatitis, liver cirrhosis, lung, kidney, ovarian, breast (mastopatie, fibroadenom).

The potential role of CA 15-3 in prognosis of breast cancer has been analyzed in a few studies, which came to inconsistent results. It has been reported that patients with elevated preoperative CA 15-3 levels had a worse outcome than patients with low levels[9]. The ASCO guidelines found the data insufficient to recommend the routine use of CA 15-3 measurements for screening, monitoring response to treatment, diagnosis, or staging. The ASCO guidelines recognized that in the absence of readily measurable breast cancer, an increasing CA 15-3 might be used to suggest progression of disease.

Our aim was to investigate the association of CA 15-3 concentrations with clinicopathological parameters and outcomes in patients with breast cancer.

PATIENTS AND METHODS

In a retrospective study, we investigated the association of the serum levels of CA 15-3 with tumor characteristics as prognostic factors of the disease.

The study population enrolled a total of 586 consecutive participants with a histologic diagnosis of breast cancer or carcinoma in situ, treated at the Department of Gynaecology of the University of Saarland between January 2010 and December 2012. Information concerning age, menopausal status, diagnosis, and clinical pathology were collected for each patient and are summarized in Table 1. The participants were monitored for tumor recurrence or death during a mean follow-up period of 17.5 months.

The breast cancer patients were staged according to TNM-UICC classification. 532 patients were diagnosed histologically with ductal infiltrating carcinoma, while 49 of carcinoma in situ. Tumor size was classified as T1 (less than or equal to 2 cm) in 297 (50.77%), T2 (tumor size between 2 and 5 cm) in 157 (26.84%), T3 (tumor size more than 5 cm) in 27 (4.62 %) and T4 (tumor extends to chest wall) in 29 (4.96 %) of the cases. There were 400 patients with negative lymph nodes and 162 patients with positive lymph nodes. Main tumor characteristics are shown in **Table 1**.

Pretreatment serum CA 15-3 measurements were available for 510 participants. CA 15-3 serum levels were evaluated at time of the

Table 1

Main clinical-pathological tumor characteristic of 586 breast cancer patients

Characteristic	Patients	Percent		Characteristic	Patients	Percent
Age < 50 years 50-70 years > 70 years	122 296 168	20.82% 50.52% 28.66%		Menopausal status Premenopausal Perimenopausal Postmenopausal Missing data	117 35 433 1	19.97 % 5.97 % 73.89 % 0.17 %
Histological diagnosis Ductal infiltrating carcinoma In situ carcinoma Missing data	532 49 5	91.57% 8.43% 0.85%		Grading G1 G2 G3 Missing data	61 339 17 69	11.80% 65.57% 22.63% 11.77%
Tumor size T1 T2 T3 T4 Missing data	297 157 27 29 76	50.77% 26.84% 4.62% 4.96% 12.96%		Nodal involvement N0 N1 N2 N3 Missing data	400 123 20 13 30	68.61% 21.10% 3.43% .26% 5.11%
Metastatic site M0 M1 Missing data	538 28 20	95.05 % 4.95 % 3.41 %		Her2-neu status Negative Positive Missing data	436 89 61	74.40 % 15.19 % 10.46 %
ER status Negative Positive	109 477	18.60 % 81.40 %		PgR status Negative Positive Missing data	213 370 3	36.35 % 63.14 % 0.51 %
Local relapse No Yes	571 15	97.44% 2.56%		Death No Yes	574 12	97.95 % 2.05 %

primary diagnosis and were not used in our study to monitor response to breast cancer treatment. The cut-off level for serum CA 15-3 was established at 30 U/ml.

The statistical analyses were carried out using Statistical Analysis System version 9.2 statistics software. The Kruskal-Wallis test was used for relating CA 15-3 levels to clinicopathological parameters. A p-value of less than 0.05 was considered to be significant.

RESULTS

Relationship between CA 15-3 and tumor characteristics in adjuvant patients

Serum levels of CA 15-3 in patients with carcinoma in situ did not differ significantly as compared with patients with invasive breast cancer (20.85 U/ml vs. 64.58 U/ml, p>>0.05).

There were significant correlations between tumor size and CA 15-3 levels in our analysis. CA 15-3 concentrations were higher in patients with larger tumors; p= 0.0377. However, patients with T4 breast cancer had lower CA 15-3 level (mean 17.72 U/ml) than patients with T1, T2 and T3 tumors.

The CA 15-3 concentrations were independent of grading, nodal burden, local disease

recurrence, ER, pgr and Her2 expression. A detailed breakdown of distribution of CA 15-3 levels in relation to tumor characteristics is shown in **Figure 1**.

*Relationship between CA 15-3 and tumor characteristics in patients with metastatic disease*

26 patients with available data had already distant metastasis at time of their initial breast cancer diagnosis as follows: 5 patients had lung metastases, 8 bone metastases, 2 liver metastases and the others had more than one location of distant metastasis. Patients with primary metastatic disease had a mean CA 15-3 level of 79.45 U/ml, significantly higher than patients without metastasis; p< 0.0001.

The relationship between tumor marker level and clinical and histopathologic characteristics of the patients is shown in **Figure 2**. CA 15-3 level seemed to be increased linearly with tumor size in patients with metastatic disease.

Figure 1

Relationship between CA 15-3 and tumor characteristics in non metastatic patients
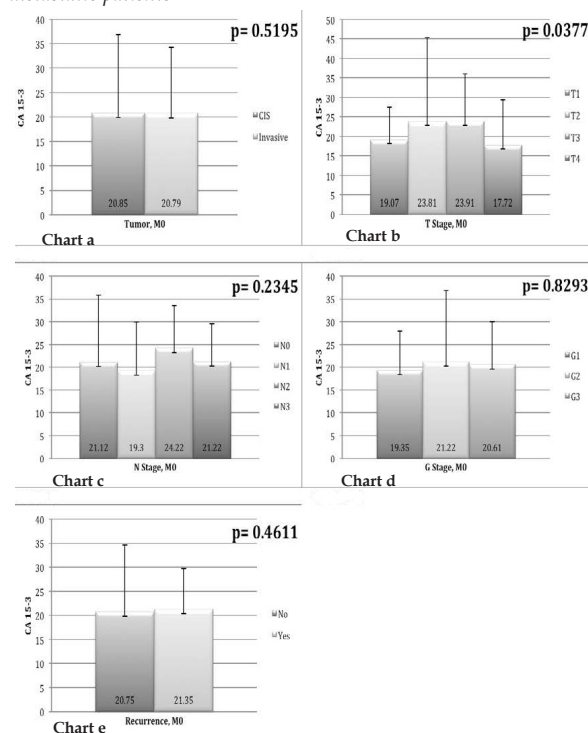
Figure 2

Relationship between CA 15-3 levels and tumor characteristics in metastatic patients
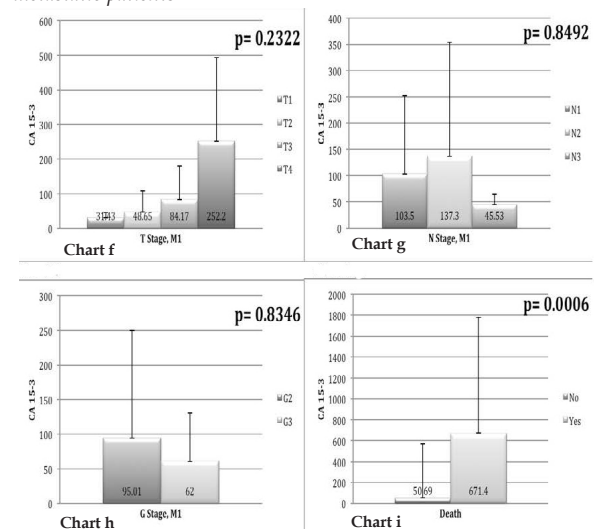

However, the observed differences of CA 15-3 levels between T1, T2, T3 and T4 tumors are not significant. Although a tendency for increased CA 15-3 levels in patients with axillary metastases was observed, this difference again did not reach statistical significance. Non-significant elevations of CA 15-3 were observed in patients with G2 and G3 tumors.

We evaluated correlation of CA 15-3 level at the time of primary diagnosis with ER, pgr and Her 2 expressions. A mean serum CA 15-3 concentration of 20.64 U/ml was observed in patients with triple negative breast cancer without metastasis, while patients with distant

metastasis had a mean level of 33.90 U/ml. Patients with hormone receptor negative, Her2/neu positive, and metastatic tumor had a mean CA 15-3 level of 23.28 U/ml. CA 15-3 levels were correlated with ER, pgr and Her2 positivity. Patients with hormone and Her2/neu receptor positive metastatic breast cancer had a mean CA 15-3 level of 54.78 U/ml. High concentrations of CA 15-3 (mean level 114.5 U/ml) were observed in patients with metastatic, hormone receptor positive and Her2/neu negative disease, significantly higher than in patients without metastasis; p< 0.0001 (**Figure 3**).

Figure 3

Relationship between CA 15-3 levels and receptor status in non metastatic and metastatic patients
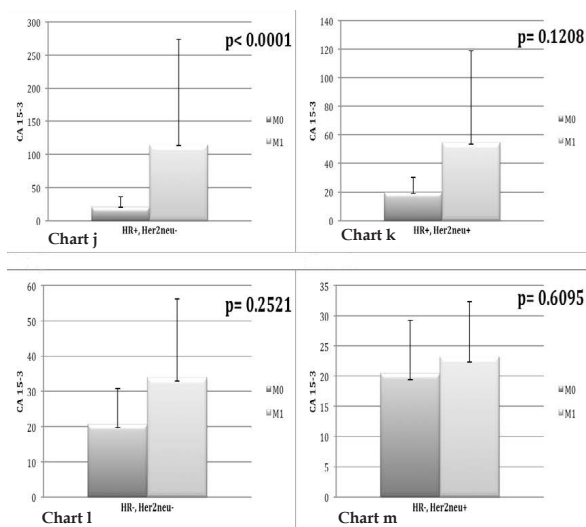
During the follow-up period, 12 patients (2.05%) died, 11 of which due to breast cancer. For 8 patients with available data, significantly higher CA 15-3 levels were found at time of diagnosis (mean level 671.4 U/ml); p= 0.0006. Out of these 8 patients, 2 patients had no distant metastasis and slightly higher CA 15-3 values (mean 27.3 U/ml) compared to survivors.

DISCUSSION

The classic prognostic markers in breast cancer such as axillary lymph node status, tumor size, histological grade, and receptor expression require tissue sampling, are costly and cannot by themselves predict the risk of development of distant metastasis and outcome in patients with breast cancer. Tumor markers that can accurately predict overall survival, which can identify the group of patients needing close follow up and those who will benefit most from adjuvant therapy, are needed. Serum CA 15-3 has been the most frequently investigated tumor marker in breast cancer.

The most important application for CA 15-3 is in monitoring therapy in patients with advanced breast cancer[15]. CA 15-3 levels have also been demonstrated to predict outcome in breast cancer[9]. However, the potential role of CA 15-3 as a prognostic marker for breast cancer was investigated only in a few studies. Our results suggest that elevated pretreatment serum marker values were correlated with poor prognosis and death from the disease.

By comparing CA 15-3 levels in metastatic and non-metastatic disease, we found a statistically significant difference between the two categories. CA 15-3 can stratify patients into high and low risk groups. Patients in the high risk group have a poor prognosis, a higher risk of distant metastasis, of death from the disease and need close follow-up and most likely benefit from adjuvant therapy.

This study demonstrates a correlation between stage of breast cancer and CA 15-3 positivity rates. The higher the breast cancer stage, the more likely the CA 15-3 level will be elevated. Our results are comparable to results from other analyses with a similar study design[7,10]. Surprisingly, the 5 patients from our study with T4 non-metastatic tumors had a significantly lower CA 15-3 level in our analysis. A normal result does not prove absence of cancer[7,8].

The CA 15-3 level was also significantly related to death from disease. The higher the CA 15-3 levels, the poorer is the prognosis. In line with our findings, Duffy et al. Evaluated the relationship between CA 15-3 levels and patient outcome and has shown that high preoperative levels of CA 15-3 are associated with an adverse patient outcome[9]. Survival may be poorer in patients with an elevated serum marker level because of the statistically significant relationship between CA 15-3 and metastasis. Other authors have published similar observations. For example, Daniele et al., Berutti et al. And Horobin et al. Reported that high preoperative levels of CA 15-3 can predict poor outcome in patients with breast cancer[11-13]. They confirmed our findings that patients with abnormal CA 15-3 levels have a shorter disease-free interval and overall survival rate compared to those with normal levels.

We found no correlation between CA 15-3 levels and recurrences of the disease. Daniele et al. And Iaffaioli et al., however, found that patients with abnormal preoperative CA 15-3

levels are significantly associated with early recurrence of the disease[11,14].

These results confirmed that elevated preoperative serum levels of CA 15-3 are significantly correlated with the presence of distant metastatic disease. However, CA 15-3 has not been shown to be a more useful prognostic tool than the routine traditional markers. Elevated CA 15-3 level is a useful parameter for predicting clinical outcomes and it may be used collectively with these markers in the management of breast cancer.

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