Breast cancer tumor markers. A literature review

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Abstract

In the last decades breast cancer became an importanthealth problem for women all over the world. In order to improve the outcomes and increase the overall survival, appropriate follow up is needed. This is a review regarding the most important breast cancer tumor markers used in diagnostic and follow up of the patients diagnosed with this malignancy
Keywords: *breast cancer, tumor markers, CA 15-3, CA 27.29, CEA, HER*

Introduction

Unfortunately, breast cancer is a significant health problem affecting women worldwide with growing incidence over the past decades. When detected in less advanced stages, breast cancer is potentially curable thanks to the development of multidisciplinary treatment protocols including chemotherapy, surgery and irradiation. However, the most appropriate therapeutic protocol is chosen according to tumor histology, clinical and pathologic characteristics of the primary tumor, axillary node status, hormone receptor content, presence or absence of detectable metastatic disease, patient co-morbid conditions, patient age, and menopausal status[1,2].

Because of the variability in clinical progression of disease, the role of markers that could predict tumor behavior is particularly important in breast cancer. Tumor markers are useful for diagnostic procedures, staging and evaluation of therapeutic response, detection of local recurrence or distant metastasis and development of new treatment modalities[1].

In 2007, American Society of Clinical Oncology (ASCO) has made some recommendations regarding the use of tumor markers in prevention, screening, treatment and survival in breast cancer, taking into consideration indicators like overall survival, disease-free survival, quality of life, treatment toxicity and cost-effectiveness report. The following markers have been proposed: cancer antigen (CA) 15-3, CA 27.29, carcinoembryonic antigen (CEA), estrogen receptor, progesterone receptor, human epidermal growth factor receptor 2, urokinase plasminogen activator, plasminogen activator inhibitor 1, and certainmultiparameter gene expression assays[1].

CA 15-3 and CA 27.29 Markers

CA 15-3 is one of the most relevant tumor markers in breast cancer. It is an epitope of the transmembrane glycoprote in mucine 1 (MUC1), derived from the MUC1 gene. This glycoprotein has a large extracellular region, a transmembrane sequence and a cytosolic domain and is overexpressed and aberrantly glycosylated on its extracellular region in breast cancer. The MUC1 antigen shed into the bloodstream and is recognized by two monoclonal antibodies in a radio-immunoassay, therefore it can be measured in the peripheral blood by two related tests: CA 15-3 and CA 27.29. They have almost the same indications and limits, while their sensitivity and specificity are limited by a number of factors[2].

In terms of sensitivity, not all breast cancers produce MUC1 antigen. Also, in the early stages of tumor development, the levels can be quite low. As for the specificity, high levels (remaining constant in time) of CA 15-3 can be found in healthy individuals presenting a series of benign conditions like chronic hepatitis, cirrhosis, tuberculosis, sarcoidosis, hypothyroidism, megaloblastic anemia, benign breast conditions, pelvic inflammatory disease, endometriosis, systemic lupus erythematosus, pregnancy or lactation. When it comes to other malignancies associated with higher levels of CA 15-3, abnormal levels of this marker might be seen in cancers of the lung, liver, colon, ovary, endometrium or pancreas.

CA 27.29 may be elevated in malignant tumors of colon, stomach, kidney, lung, ovary, pancreas, uterus or liver. Levels which overcome the upper normal limit can be found in the first trimester of pregnancy, endometriosis, ovarian cysts, benign breast diseases or renal lithiasis.

In this regard, because the two markers measure the same antigen in the blood, only one of them is recommended to be tested[3].

The Role of CA 15-3 in Breast Cancer Diagnosis

When it comes to breast cancer, data from literature showed that a value of CA15-3 over 30 U/ml correlates with the extension of disease. High levels were found in less than 10% of patients with early disease and in about 70% of patients with advanced disease. Sensitivity and specificity are considered to be higher for metastatic or recurrent disease.

A study realized in a Jordanian hospital included 136 women, from which 45 were healthy, 72 were diagnosed with breast cancer and 19 had benign le-

Received:
January 08, 2015
Revised:
February 19, 2015
Accepted:
February 27, 2015

sions of breast. Serum concentration of CA 15-3 was significantly higher in breast cancer patients (37.65) than in healthy individuals (14.07) and women with benign diseases (12.3), but a significant association between serum CA 15-3 concentration and the age of cancer onset, the age of installation of menarha, the age of installation of menopause or parity could not be found. Patients with breast cancer receiving hormone therapy or pills were significantly associated with low levels of CA 15-3. Significantly raised concentrations have been found in patients presenting grade II and III or stage II and III breast cancers[4].

The Role of CA 15-3 in Establishing the Prognostic of the Disease

Regarding the use of CA 15-3 and CA 27.29 in the evaluation of prognosis, ASCO does not recommend routine testing because of the lack of clinical trials that demonstrate its benefit. However, there are some studies that indicate the probability that they have prognostic value[1].

One of them is a retrospective study realized by Velaiutham and contributors in order to establish a correlation between preoperative values of CA 15-3 on the one hand and the stage of the disease and the overall survival of the breast cancer patients on the other hand. In this study 437 women were evaluated at presentation between January 1999 and October 2003. A concentration of CA 15-3 >51U/ml was found in 0% of patients in stage I, 7.9% of patients in stage II, 36.7% in stage III, 68.6% in stage IV. A subset of 331 patients which had data about survival showed that normal CA 15-3 values were correlated with a 5 year survival of 85% while cases with high values reported a survival rate of only 38%. At serum concentrations of CA 15-3 >200 U/ml the 5 year survival was 28%. The study concluded that serum CA 15-3 concentration at presentation is important, is an independent prognostic factor and, if very high, it can justify searching for metastases[5].

A prospective study performed in 2010 by Molina has showed the utility of CEA and CA 15-3 as prognostic factors in primary breast cancer, using a group of 2062 patients, diagnosed between 1984 and 2008. Concentrations of CEA>5 μg/L and CA 15-3 >30 kU/L were found in 12.7% and 19.6% of patients and one or both tumoral markers were elevated in 28% of cases.

A raise in each of them was correlated with a greater size of the tumor and lymph node involvement. Tumour size, estrogen receptor and CEA were independent prognostic factors through multivariate analysis in the total group, as well as in the group of patients with and without lymph node involvement.

Adjuvant treatment and CA 15-3 proved to be independent prognostic factors only in patient with no lymph node involvement. The study concluded that CEA and CA 15-3 represent useful prognostic factors in cases with breast cancer with or without lymph node involvement. In the mean time CEA >7.5 μg/L was associated with a higher probability of sub-clinic metastases[6].

In their study, Tarhan et al. included 30 patients in whom circulant tumor cells and CA 15-3 were measured at the moment of metastatic disease diagnosis. The overall survival of cases with CA 15-3>108 ng/dl was 19 months, compared with 62 months for cases with normal seric levels. Cases presenting higher number of circulant tumor cells reported an overall survival of only 19 months, while in the other cases the overall survival reached 40 months. The differences between the two groups were statistically significant[7].

A case control study conducted in Iraq between October 2009 and February 2011 involved blood tests coming from 30 women diagnosed with breast cancer, before treatment. Another series of blood tests were taken after 3 cycles of chemotherapy. A statistical significance was also observed between the tumor mass, the tumor stage and the levels of CA 15-3. After 3 cycles of chemotherapy, CA 15-3 significantly decreased. Cases that developed recurrences had a significantly higher concentration. Therefore, this study showed that CA 15-3 represents an important marker of diagnosis and prognosis especially when it comes to recurrence detection[8].

The Role of CA 15-3 in Treatment Monitoring

According to ASCO, there are no sufficient data to sustain that CA 15-3 and CA 27-29 can be monitored through the response to treatment. They can be used in association with clinical examination and imagistic studies in order to evaluate this response. It is still a matter of debate whether they have any role in establishing which would be the best therapeutic option for each patient. However, ASCO does not recommend their monitoring in order to detect recurrences[1].

The first study which demonstrated the possibility of early detection of the recurrence by dosing tumor markers was the one conducted by Jager. He included in his study patients with increased values of CA 15-3 and CEA but with no clinic sign of recurrence. Patients submitted to treatment developed recurrences after a mean time of 36 months, while those who did not receive any treatment developed recurences after a mean time of 4 months[9].

A study conducted by Nicolini and contributors compared the sensibility and specificity of various tumor marker in order to detect recurrence. Comparisons were done between different cut-off values of MCA (cut-off>11 vs. cut-off>15 U/ml) and CEA, and CA 15-3. At a cut-off 11 U/ml, association between MCA - CA 15-3 had a higher sensibility but a lower specificity, accuracy and a lower predictive value[10].

Into another study, conducted by Kovner et al. patients presenting increasing CA 15-3 values were submitted to tamoxifen treatment and results were compared with a similar subgroup who did not receive any treatment. After 11 months follow up, 29% of untreated patients reported recurrences while in the group submitted to Tamoxifen protocol no one develo-

ped recurrence[11]. Although all these studies have been conducted on small series of patients, all suggest the idea that whenever increased level of CA 15-3 appear, therapeutic protocols should be implemented even in cases without any clinical signs of disease.

When it comes to CA 27.29, it should be dosed every 6 weeks in order to estimate the therapeutic response; once remission is obtained, CA 27.29 should be dosed every 3 months[11,12].

Another utility for both markers is evaluation of treatment response of bone metastases ; sometimes they can by more difficult to be monitorised by radiological studies. A study conducted in Ireland evaluated the utility of CA 15-3 dosage as an alternative to bone scintigraphy.

The study included 218 patients and developed on a four years period. CA 15-3 was monitored every 3 months, while bone scintigraphy was performed annually or in the moment of developing clinical symptoms. The study concluded that CA 15-3 had a sensibility of 81.5%, specificity of 66% and positive predictive value of 92%[13].

Whenever association between increased CA 15-3 and apparently normal imagistic studies is found, an active follow-up is needed.

CEA

CEA is not routinely recommended for screening, diagnostic, stadialization or monitoring treatment response in patients with breast cancer.

However, increased values might appear in metastatic disease or in cases in which treatment is inefficient. It should not be omitted the fact that false positive results might appear during the first 4-6 weeks after treatment[1].

A study conducted by Moazzezy et al. included 60 Iranian women, which were rendered in 2 groups: a group of 30 patients diagnosed with breast cancer who weren't submitted to neo-adjuvant chemotherapy or hormonal therapy and a control group of 30 healthy women. CEA and CA 15-3 were dosed using ELISA tests. Serum concentrations of CEA and CA 15-3 were significantly higher in the subgroup presenting breast cancer: 5.0033 μg/L, 178.1667 U/ml respectively and only 1.1237 μg/L, 21.13 U/ml respectively in the healthy women group. When it comes to CEA concentration, a statistical significant difference was established between its' concentration and tumor degree. Between the 2 markers, a weak correlation was established[2].

A Korean study published in 2014 showed that association between CA 15-3 and CEA can provide a sensibility rate of up to 80.7%; the same study demonstrated that association of thioredoxin 1 can increase the sensibility rate up to 97% (Figure 1)[14].

A study conducted in 2013 by San-Gang Wu evaluated the prognostic value of pre-operative concentrations of seric CEA and CA 15-3 in patients with breast cancer. A total of 470 patients diagnosed with breast cancer were included; increased values of CEA and CA 15-3 were seen in 34 (7.2%) respectively 58 (12.3%) cases. These values seemed to be positively correlated with tumor dimensions and axillary lymph node status.

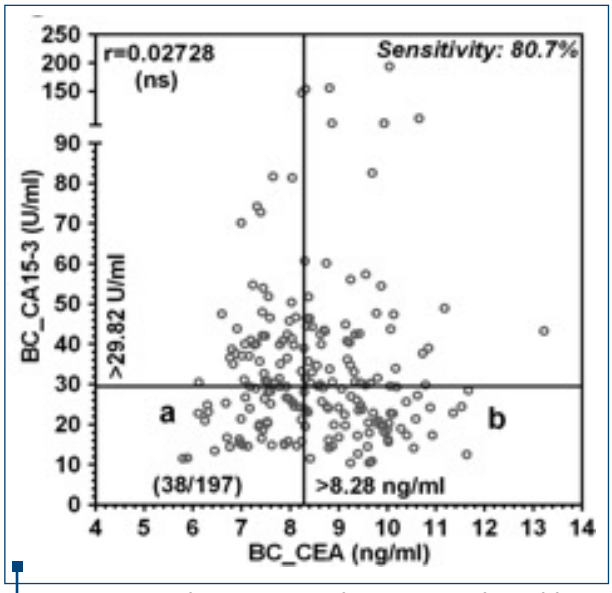

Figure 1. Association between CA 15-3 and CEA can increase the sensibility

Another interesting correlation obtained in this study was association between triple negative breast tumors and lower levels of CEA (p=0.002).

Metastases free survival, disease free survival and overall survival were higher in patients with normal levels of CEA when compared to those with increased values: 84.1% vs. 54.5% (p<0.001), 82.7% vs. 54.8%, and 89.7% vs. 78.5%, respectively. The same parameters (metastases free survival, disease free survival and overall survival) were also correlated with CA 15-3 levels.

At a 5 year follow up patients with normal values reported an improved outcome when compared to those with increased tumor markers values: 84.0% vs. 69.6%, 83.0% vs. 66.2%, 90.9% vs. 74.2%, respectively[15].

Estrogene and Progesterone Receptors

Estrogene and progesterone receptors should be measured in both primary breast tumors and metastatic disease in order to determine whether the patient is an appropriate candidate for hormonal therapy. The increased content in hormonal receptors of the tumor cells is associated with an improved prognostic due to the possibility of association in the therapeutic protocol of hormonal therapies such as tamoxifen, aromatasis inhibitors or irreversible inhibitors of estrogenic receptors.

All these drugs can be used in order to prevent recurrence and to treat metastatic disease[1].

Proliferation Markers

Actual data are insufficient in order to recommend utilization of proliferation markers identified by flow cytometry[1].

HER2

HER2 is a derived epithelial growth factor oncoprotein classified as circulant tumor marker which can be detected by histochemical or genetic tests of the tumor tissues.

Its presence can influence the choice of the most appropriate chemotherapeutic protocol.

Patients diagnosed with HER2 positive breast cancer can benefit from the association between monoclonal antibodies such as trastuzumab, which has a targeted action on HER2 molecules and antacycline based chemotherapy.

The presence of HER2 oncoprotein is usually associated with poor response at endocrinologic treatment including tamoxifen, chemotherapic treatment such as cyclofosfamide, metothrexate or 5 Fluorouracil but with positive response at antracyclines, paclitaxel or monoclonal antibodies like trastuzumab or lapatinib.

Extracellular circulant domain of HER 2 was proposed as surrogate marker in order to provide an early detection of recurrence or for monitoring the treatment response.

The extracellular domain can be detected in serum or plasma utilizing ELISA tests and is positive in up to 30% of patients with metastatic disease[(1)].

P53

Existent data are insufficient to recommend routine determination of P53 in managing patients with breast cancer. It is thought that the anomalies of P53 gene can be associated with tumor resistance at various therapies[(1)].

Urokinase Plasminogen Activator (uPA)/ Plasminogen Activator Inhibitor (PAI-1)

They can be dosed by ELISA technique on a minimum mass of 300 mg of breast tumor in order to predict prognosis in patients newly diagnosed with breast cancer, with no lymph node involvement. However the imunohistochemical diagnosis is not accurate enough and ELISA test on smaller specimens has not been approved yet. Further studies are still going in order to establish the predictive role of these markers and their utility in choosing the most appropriate therapeutic protocol[(1)].

D Cathepsin

D cathepsin can be dosed in the cellular cytosol by radiometric methods or by immunohistochemistry. However, further studies are still needed in order to introduce this marker in the standard protocol in diagnosis and follow up of the patients with breast cancer[(1)].

Conclusions

The main disadvantage of serum markers for breast cancer is the lack of sensitivity for early stages. However, CA 15-3 seems to be the most appropriate marker in diagnosis and follow up in women diagnosed with breast cancer. Otherwise, unfortunately, many patients are still diagnosed in an advanced stage of the disease. Hence, intensive studies are needed in order to determine the best prognostic factors and the correlation between breast cancer tumor markers and different therapeutic agents. In this way, a better control of the disease and an increased overall survival might be obtained. ■

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