Preoperative CA 15.3 and prognosis in primary breast cancer

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CA15.3 is a breast cancer-associated antigen encoded by the MUC-1 gene. The clinical applications of CA 15.3 are the monitoring of response in advanced breast carcinoma and the early detection of recurrences. We have investigated the prognostic value of CA 15.3 in primary breast cancer. Preoperative serum CA 15.3 was measured in 478 patients with early breast cancer. Positive CA 15.3 was defined as > 30 U/ml. CA 153 positivity was correlated with patient outcome in terms of disease-free survival (DFS). Seven per cent of patients had elevated serum CA 15.3. A positive association was found between CA 15.3 positivity and tumour size. Twenty-one per cent of the patients with T3 and T4 tumours had high serum concentrations of CA 15.3; while only six per cent of patients with T1 and T2 tumours had elevated concentrations of CA 15.3 (p < 0.0001). There was no correlation between CA 15.3 serum levels and menopausal status, axillary lymph node status, estrogen receptor status, p53 and erbB-2 status, and CEA serum levels. With a median follow-up of 24 months, we found that elevated CA 15.3 levels predicted a poor clinical outcome. The probability of disease-free survival at two years was 75% in patients with high preoperative CA 15.3 compared with 90% in patients with normal CA 15.3 levels (log-rank p = 0.005). The association of CA 15.3 with DFS was also analysed with a Cox analysis, and was found to be independent of tumour size. The multivariate analysis showed that poor disease-free survival was significantly associated with high CA 15.3 (p = 0.04), large tumour size (p = 0.001), estrogen receptor negative status (p = 0.008), overexpression of erbB-2 (p = 0.04), and overexpression of p53 protein (p = 0.05).

Preoperative serum CA 15.3 is significantly related to clinical outcome in patients with early breast cancer. High CA 15.3 indicates a poor prognosis and this is independent from tumour size. Whether the poor prognosis associated with CA 15.3 is related with the role of mucins in the adhesion of cancer cells needs to be investigated.

Key words: CA 15.3, breast carcinoma, disease-free survival, prognosis, mucin, MUC-1.


CA 15.3 preoperatorio en el pronóstico del cáncer de mama primario

El CA 15.3 es un marcador tumoral, producto del gen MUC-1, utilizado para la monitorización del tratamiento en cáncer de mama avanzado y la detección precoz de las recurrencias. Este estudio ha explorado el valor del CA 15.3 en el pronóstico del cáncer de mama primario.

Se determinaron los niveles séricos preoperatorios de CA 15.3 en el suero de 478 pacientes con cáncer de mama primario, correlacionándolos con la evolución de las pacientes, evaluada en términos de supervivencia libre de enfermedad.

Un 7% de las pacientes presentó elevación de CA 15.3 en el suero (> 30 U/ml). La elevación preoperatoria de CA 15.3 se correlacionó de manera muy significativa con el tamaño tumoral. El 21% de los pacientes con tumores T3 y T4 presentaron niveles elevados de CA 15.3, frente al 6% en el grupo de pacientes con tumores T1 y T2 (p < 0.0001). No hallamos correlación entre los niveles de CA 15.3 y el estado menopáusico, la afectación ganglionar axilar, la expresión en tejido tumoral de receptores estrógenicos, p53, o erbB-2, ni con los niveles séricos de CEA.

Los niveles elevados de CA 15.3 fueron un factor pronóstico desfavorable. Las pacientes con niveles altos de CA 15.3 tuvieron una supervivencia libre de enfermedad (SLE) significativamente peor que las pacientes con niveles normales de CA 15.3. A los 2 años la estimación de SLE era del 75% en las pacientes con CA 15.3 positivo y del 90% en las CA 15.3 negativa (log-rank, p = 0.05). El CA 15.3 tuvo, además, un valor pronóstico independiente en el análisis multivariante. El análisis de Cox de la SLE mostró la significación estadística de CA 15.3 elevado (p = 0.04) y de los siguientes factores: tamaño tumoral mayor (p = 0.001), receptores estrógenicos negativos (p = 0.008), sobreexpresión de erbB-2 (p = 0.04), y acúmulo de p53 (p = 0.03).

La determinación preoperatoria de los niveles de CA 15.3 tiene valor pronóstico en las pacientes con cáncer de mama primario, y puede representar un factor de selección para tratamientos específicos dirigidos contra la mucina MUC-1.

Palabras clave: CA 15.3, cáncer de mama, supervivencia libre de enfermedad, pronóstico, mucina, MUC-1.
INTRODUCTION
Breast cancer is the most common malignancy and the first cause of cancer death in women. The prognosis of breast cancer is related to the extent at diagnosis and biochemical markers of tumour invasiveness and aggression[1,2]. Although less than 10% of patients have advanced disease at diagnosis, more than 50% of cases eventually recur[3].

A great effort has been done for improving this results in order to identifying prognostic factors that could be used in the treatment selection. CA 15.5 is a breast-associated antigen encoded by the MUC-1 gene, and is also called PEM (polymorphic epithelial mucin). CA 15.5 is widely used as a tumour marker in patients with breast carcinoma. Approximately 80% of the metastatic breast cancer patients have high CA 15.5 levels[4], while less than 10% of early breast cancer patients have high CA 15.5 serum levels[5].

The main clinical applications of CA 15.5 are the monitoring of patients with metastatic breast carcinoma undergoing treatment[6] and the preclinical detection of recurrences[7]. CA 15.5 has been associated with a poor prognosis in metastatic breast carcinoma[8,9]. The objective of this study was to establish whether preoperative serum CA 15.5 is a prognostic factor in early breast cancer.

PATIENTS AND METHODS
We studied patients with primary breast cancer diagnosed between 1992 and 1994 in the Hospital Universitario 12 de Octubre. Patients were excluded if they had metastatic breast cancer at the time of diagnosis or if they develop metastasis in the first 5 months after surgery.

The studied variables were CA 15.5 serum levels, menopausal status, axillary lymph node status, tumour size, estrogen receptor status, over-expression of erbB-2 and p53 in tumoral tissue, and CEA serum levels.

Serum levels of CA 15.5 and CEA were determined by an enzyme-immunoassay of microparticles (MEIA) in a IMX autoanalyzer (Abbott). The CA 15.5 normal cut-off value was <30 U/ml for CEA we used as a cut-off value <5 ng/ml. Thirty U/ml was used as a cut-off following the manufacturer recommendations. Estrogen receptor status was determined on tumour cytosols using a commercially available enzyme-immunoassay (Abbott ER-EIA monoclonal); the normal value was established in <20 fmol/mg protein. The erbB-2 expression was determined by ELISA (Oncogene Science) in tumour tissue using as normal value <14 HNU/mg protein; expression of p53 was evaluated by western-blot, using the antibody pAb 181 (Oncogene Science); p53 positivity was defined according to controls (Montero S, et al; manuscript in preparation).

Chemotherapy was administered to all patients with axillary node involvement, in node negative premenopausal patients with tumour size >1 cm, and in postmenopausal patients with negative estrogen receptor (ER). Tamoxifen was given to all patients with positive ER. Radiation therapy was administered in cases treated with conservative surgery and in patients with four or more axillary nodes. All patients were followed postoperatively. Clinical examinations were performed every 3 months for the first 2 years, every 6 months for the next 5 years, and annually thereafter. Mammography was performed at least every 2 years. These follow the published recommendations for the follow-up in breast cancer patients[10]. Other investigations directed at detecting recurrences were performed if indicated clinically.

The association between CA 15.5 levels and the clinicopathologic characteristics was evaluated using the Chi-square test, using the Mantel-Haenszel test to assess for linear association. The Kaplan-Meier estimate was used to calculate disease-free survival (DFS) and log-rank test was used to make comparisons. For multivariate analysis, the Cox proportional hazards regression model was used selecting the variables which showed statistical significance in the univariate analysis.

RESULTS
We studied 478 patients with primary breast carcinoma (stage I-III). Median age was 58 years (range, 26-86). Thirty-eight per cent of the patients were premenopausal, and 62% were postmenopausal. The majority of the carcinomas were invasive ductal carcinoma, 10% were invasive lobular carcinomas, and 2% had other histologies. Eighty-three per cent of the patients had T1-T2 tumours and 17% had T3-T4 tumours. Forty-nine per cent of the patients were node negative and 51% were node positive. The number of axillary lymph nodes involved at diagnosis ranged from 0-51 (median 5). Sixty-eight per cent of the cases were ER positive, and 32% were ER negative. Fifty-six per cent of the cases were p55 negative, while 18% were p55 intermediate, and 26% were p55 positive. ErB-2 was overexpressed in 16% of the patients and negative in 84%. CEA serum levels were normal in 92% of the patients, and positive in 8%. High serum levels of CA 15.5 were found in 8% of cases, and the remaining 92% had normal levels of CA 15.5.

Post-surgical adjuvant therapy was hormonal therapy alone in 50% of the patients, chemotherapy plus hormonal therapy in 32%, chemotherapy alone in 21%, radiotherapy alone in 5%, and no adjuvant treatment in 3% of cases.

Table 1 shows the correlation between serum CA 15.5 levels and the recorded clinicopathologic and biochemical characteristics. There was a significantly correlation between high CA 15.5 levels and tumour size. Twenty-one per cent of the patients with T3-T4 tumours had high CA 15.5 serum levels compared with 6% in the T1-T2 group of patients (p<0.0001). In contrast, there was not a correlation between CA 15.5 and menopausal status, lymph node status, estrogen receptor status, overexpression of erbB-2 in tumour tissue, expression of p53, or CEA serum levels.

When we analyzed survival curves by the Kaplan-Meier method, we found a significant relation between poor disease-free survival and positive CA 15.5, larger tumour size, positive axillary lymph node status, negative ER status, overexpression of erbB-2, and p55