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Post-Operative Follow-up of Breast Cancer Patients Using Serum Tumor Markers: CEA and CA15.3 vs MCA in the Early Detection of Distant Metastases

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Abstract: In breast cancer current guidelines do not recommended the routine use of serum tumor markers. Differently, we observed that CEA, CA 15.3 panel permits early detection for most relapsing patients. As high sensitivity and specificity and different cut-off values have been reported for Mucin-like Carcinoma associated Antigen (MCA), we compared MCA with the above mentioned tumor markers. In 150 breast cancer patients submitted to post-operative follow-up with tumor markers, we compared MCA (cut-off values, = 11 and = 15 U mL^{-1}) with CEA and CA15.3 for detection of relapse. Distant metastases occurred in 12 (8%) of the 150 patients who were disease-free at the beginning of the study. MCA sensitivity with both cut-off values was higher than that of CEA or CA15.3 (65 vs 12%, 33%) and (55 vs 17%, 31%), respectively. With cut-off = 11 U mL^{-1}, MCA showed the lowest specificity (32%). With out-off =15 U mL^{-1}, MCA specificity was lower than that of CEA and CA 15.3 (71 vs 95 and 96%, respectively). At both the evaluated cut-off values serum MCA sensitivity is higher than that of CEA or CA15.3 but its specificity is lower than them. These findings further support the need for prospective randomized clinical trial to assess whether post-operative follow-up with an appropriate use of serum tumor markers such as MCA can significantly improve clinical outcome of early detected relapsing patients.

Key words: Breast cancer, CEA, CA15.3, MCA, metastases

INTRODUCTION

In breast cancer patients, current guidelines post-operatively recommend mammography at regular intervals and not routine use of any instrumental or laboratory test for early detection of relapse and monitoring of metastatic disease. In fact, in randomized trials and meta-analysis post-operative follow-up has been shown to be useful only in early diagnosis but not in improving clinical outcome and/or quality of life (Smith *et al*., 1999). Different studies appropriately using serum tumor markers within post-operative follow-up showed that in many relapsing patients clinical-instrumental diagnosis was anticipated and that this anticipation permitted an earlier treatment which significantly prolonged disease-free survival and/or overall survival (Nicalini and Carpi, 2000). Therefore, unlike current guidelines, it is routine practice to carry out post-operative follow-up of breast cancer patients using serum tumor markers.

Carcinoembryonic Antigen (CEA) and breast cancer associated 115D8/DF3 (CA15.3) antigens are the serum tumor markers commonly used for post-operative monitoring of breast cancer (Smith *et al*., 1999) although many other tumor markers have been investigated (Kopczynsky, 1998). We reported sensitivity for CA15.3 is higher than that of CEA (Naghshvar, 2007).

CA15.3 is one of the mucin-like biomarkers which also recently have been reported among the most useful markers to detect and monitor metastatic breast cancer (Seregni *et al*., 2004). The Mucin-like Carcinoma associated Antigen (MCA) is another widely used test to assay MUC-1. When it has been used alone, high sensitivity and specificity have been reported (Merimsky *et al*., 1991). Besides conflicting data have been found both as to MCA sensitivity and specificity compared to CA15.3 and usefulness (Pectasides *et al*., 1996). Therefore, in this study we compared sensitivity and specificity of MCA (with two commonly used out-off values: = 11 and = 15 U mL^{-1}) with that of CEA, CA 15.3 for early detection of relapse.

MATERIALS AND METHODS

From April 2004 to April 2007, 150 breast cancer patients aged 32 to 75 year (Median 51.6) were submitted to post-operative follow-up with serial serum

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determination of CEA, CA15.3 and MCA. At entry 138 patients (92%) were disease-free (Mo) and 12 (8%) showed distant Metastases (M1). At the post-operative histology 41 of the 138 disease-free patients were N+ while the 97 remaining were N-. Soon after primary surgery, all Estrogen (ER) and/or Progesterone Receptor (PgR) positive patients received hormone therapy. Moreover, all N+ and N- disease-free patients, consistent with the current international guidelines, received adjuvant chemotherapy. As to the interval time of post-operative monitoring, patients were divided into 2 groups: at low and at intermediate-high risk of recurrence according to whether they were N-PgR + or N+ and/or PgR-(N+ PgR +, N+ PgR-, N-PgR-), respectively. Axillary lymph-nodes (N+/N-) and progesterone (PgR + /PgR) status were used to divide patients into two different risk groups as they are commonly reported among the principal prognostic factors for relapse (Gold Hirsch, 2005). The 65 low risk patients underwent control visits every 6 months and the remaining 85 with intermediate-high risk of recurrence every 4 months. Post-operative follow-up was 17±7 months (m±sd). At each control visit, history, routine lab and serum CEA, CA15.3 and MCA measurement were carried out.

As to other conventional instrumental examinations, Bone Scintigraphy (BS) and Liver Echography (LE) have been reported to be more accurate Chest X-Ray (CXR) to early detect recurrences (Nicolini *et al*., 1997).

The reason for serial BS, LE and CXR examinations was to detect asymptomatic relapses falsely negative with serum tumor markers, which as we have previously reported (Nicalini and Carpi, 2000) are about 15-25% using CEA and CA15.3 tumor markers.

Patients suspected of relapse with CEA-CA15.3 tumor marker panel immediately underwent the standard radiological examinations (BS, LE and CXR). If these examinations were pathological or equivocal, patients immediately were selected to be further investigated as follows. All hot spots on the bone scintigraphy with an equivocal interpretation were examination by computed tomography and/or Magnetic Resonance Imaging (MRI). The lesions that were considered equivocal by conventional chest X-ray were clarified by computed tomography or bronchoscopy and cytologic study. The lesions felt to be equivocal at liver echography were clarified by computed tomography or fine needle aspiration cytology guided by liver echography when possible.

Serum CEA, CA15.3 and MCA concentration were measured in fasting patients by commercial immunoenzimatic assays Roche Diagnosis CS/Manheim (Germany) for CEA-CA15.3 and MCA. The within and between assay coefficients of variation for CEA, CA15.3 and MCA were all less than 4%. Serum levels > 7 ng mL^{-1} and > 32U mL^{-1} were considered to be elevated for CEA and CA15.3, respectively; for MCA = 11 and = 15 U mL^{-1} cut-off values were considered. We identified the causes of false positive tumor marker increase (Cooper *et al*., 1989). As previously described (Nicalini and Carpi, 2000), a dynamic valuation of tumor markers was made and in cases of a high tumor marker value a further blood sample was drawn two weeks to a month after the previous elevated value. If the re-measured tumor marker value had decreased to a normal value, the initial elevated value was considered to be an Isolated Elevated Value (IEV) (Andrea *et al*., 2006). The elevated tumor marker was considered to be Progressive (PI) when it was 30%, or more, higher in the sample which followed the initial elevated value (Andrea *et al*., 2006). Otherwise, two equally high values were regarded to be a constant elevation CE (Andrea *et al*., 2006). Only CE and/or PI were considered a significant tumor marker increase (Andrea *et al*., 2006).

As previously reported (Andrea *et al*., 2006) in our study, only patients with CE or PI in one or more tumor markers, clearly unexplained by any other condition, are considered suspected of tumor relapse.

Tumor marker lead time was the time from the suspicion of relapse with serum tumor marker to confirmation of relapse by radiological examinations (Andrea *et al*., 2006). When a clinically disease-free patient was suspected of relapse by re-testing of tumor markers at the regular control visit, 15 to 30 days were necessary to carry out the common (bone scintigraphy, liver echography, chest X-ray) and in case of their equivocal results, more accurate radiological examinations (CT, MRI) to confirm or rule our the suspicion (Andrea *et al*., 2006). Radiological investigations performed during this 15 to 30 days interval time and confirming the initial suspicion by tumor markers were considered as they had been performed at the same time of tumor marker re-testing; therefore in this case tumor marker lead time as computed as zero. When a patient became suspected of metastases by symptoms before the routine testing of serum tumor marker (i.e., in the interval between two regular control visits), at this time immediately the entire planned procedure was carried out to confirm or rule out the suspicion. Again, as above mentioned, the time necessary for the entire procedure took about 15-30 days and this interval time was not considered for the calculation of the tumor marker lead time. In fact, when suspicion of metastases was confirmed by radiological examination and not by tumor marker panel, tumor marker panel was considered falsely

negative. When suspicion of metastases was confirmed by radiological examinations and by tumor marker panel as well, the tumor marker panel lead time was considered zero if symptoms suspicious of metastases had appeared at the same time the entire procedure for confirmation was started; if symptoms suspicious of metastases had previously appeared, clinical symptoms only were considered the first signal of relapse and tumor marker panel was considered falsely negative.

RESULTS

During the post-operative follow-up distant occurred in 12 (8%) of the 150 disease-free patients. The organs initially involved in the relapse were: bone (Naghshvar, 2007), viscera (Seregni *et al*., 2004), soft tissue, bone and viscera (Smith *et al*., 1999). The number of the lesions was:< 3, >3<10 and > 10 in 8, 3 and 1 relapses, respectively. MCA sensitivity with both cut-off values was higher than that of CEA or CA15.3 (65 vs 12, 33%) and (55 vs 17, 31%), respectively.

MCA cut-off value = 11 U mL^{-1}. MCA, CEA and CA 15.3 were the first finding in 2 to 10 relapses. In 4 relapses for MCA and in 1 for CEA the tumor marker increase was the only sign. In 4 relapses for MCA, in for CEA and in all 2 and 3 relapses for CA15.3, respectively the tumor marker increase was concomitant with the increase of other markers and/or with clinical or instrumental findings. BS alone or combined with tumor markers (one or more) as the first finding of relapse more frequently than LE or clinical symptoms (4 vs 1 and 2 relapses, respectively).

MCA cut-off value = 15U mL^{-1}. MCA, CEA and CA15.3 were the first finding in 3 11 relapses. In 1 relapse for MCA and for CEA the tumor marker increase was the only sign. In 5 relapses for MCA, in 2 for CEA and in all 5 and 6 relapses for CA15.3, respectively the tumor marker increase was concomitant with the increase of other marker and/or with clinical or instrumental findings. Again, BS alone or combined with tumor marker increase was the first finding of relapse more frequently than LE or clinical symptoms (4 vs 2 and 3 relapses, respectively).

CE and/or PI occurred in 7 patients for CEA and in 5 patients for CA15.3. Diabetes and/or hepatic steatosis (4 patients), smoking (3 patients) for CEA, chronic liver failure (1 patient), diabetes and/or hepatic steatosis (3 patients) for CA15.3 were the concomitant conditions probably responsible for these two kinds of tumor marker increase. Significant increases for unknown reasons (false positive) occurred in no patient for CA15.3 an in 1 patient for CEA. Therefore, specificity was (100%), 100, 83 and 92% for CEA, CA15.3 and MCA (= 11 or = 15 U mL^{-1} cut-off value), respectively, when an accurate history was taken into account. Without an accurate history, specificity was 99, 96, 39 and 71% for CEA, CA 15.3 and MCA (= 11 or = 15 U mL^{-1} cut-off value), respectively.

DISCUSSION

MCA sensitivity for early detection of relapses, either with = 11 or = 15 U mL^{-1} cut off value, was higher than that of CEA or CA15.3. With regard to CEA and CA15.3, CA15.3 (with MCA cut-off value = 11 UI mL^{-1}) was more sensitive than both remaining indicators. In other studies a range of MCA sensitivity similar to CA15.3 and no significant increase in sensitivity when MCA was combined with CA15.3 were found (Garcia *et al*.,1990). These findings and our results suggest that, although MCA and CA15.3 recognise distinct epitopes on the same molecule (Daly *et al*., 1992) in metastatic breast cancer cells MCA expression almost completely overlaps that of CA15.3, while it partially occurs among CEA and CA15.3.

Total rate of significant increases of MCA was higher (= 11 or = 15 UI mL^{-1} cut-off value, respectively) than that of CEA and CA15.3. This finding does not confirm that MCA specificity is similar to or higher than that of CEA and CA15.3 (Merimsky *et al*., 1991). Moreover, our results show that in non relapsed patients the aspecific reasons probably responsible for MCA. The addition, at each control visit, of an accurate history and laboratory examinations to the dynamic evaluation of tumor markers increased their specificity while sensitivity remained unchanged. Nevertheless, in all of them CE and/or PI in one or more markers could be referred to a pending relapse rather than to the concomitant benign pathology. Conversely, among the non relapsed patients those falsely suspected with all evaluated tumor markers particularly MCA and their combination strongly decreased. In fact, CE and/or PI, unexplained by a clear concomitant benign pathology, ranged from 0% for CA15.3 to 15% for MCA with = 11 cut-off value.

Being confined to bony skeleton is considered a favourable prognostic factor for metastatic disease (Koizumi *et al*., 2003). In a general metastatic population at the presentation bony skeleton as dominant site and oligometastatic disease have been reported to involve about 15% (Vici *et al*., 2002) and 5-10% (Koizumi *et al*., 2003) of patients, respectively.

CONCLUSION

In conclusion, data from this study point out that at both the evaluated cut-off values serum MCA sensitivity is higher than that of CEA and CA15.3. However, MCA specificity is the lowest and they are both much lower

than those of CEA and CA15.3. Despite a higher sensitivity, this low specificity represents an important limitation for a meaningful clinical applicability of MCA as single marker. These findings further urge the need for randomized clinical trial to asses whether an early signaling and treatment of distant metastases with an appropriate use of serum tumour markers also can significantly improve overall survival.

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