Role of Tumor Markers and Circulating Tumors Cells in the Management of Breast Cancer

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Along with various imaging modalities, serologic tumor markers such as CA 15-3 and CA 27.29 have been used for decades to monitor treatment response in patients with metastatic breast cancer (MBC). Despite the frequent use of these markers, they lack high sensitivity and specificity for breast cancer progression. The prognostic significance of these markers remains indeterminate because of the conflicting outcome of many clinical trials. The circulating tumor cell (CTC) test has recently been studied in clinical trials in patients with MBC. Some of the studies showed that high levels of CTCs are correlated with poor survival in MBC. An intergroup trial is underway to determine the implication of changing treatment based on the CTC level. This article will discuss the current data on these markers, with special emphasis on the CTC test. The potential clinical utility of these markers will also be discussed.

Breast cancer is the most common malignancy (excluding skin cancer) affecting women in the United States and is second to lung cancer as a cause of cancer-related mortality.[1] In addition to screening, the emergence of new therapeutic agents has contributed to the significant reduction of breast cancer mortality since 1990.[1] Treatment of metastatic breast cancer (MBC) imposes a challenge to medical oncologists, as it is an incurable disease. Patients are usually treated until disease progression or unacceptable toxicity ensues. Assessment of disease progression is critical, not only to eliminate ineffective therapy, but also to avoid unnecessary toxicity.

THE ISSUE
What is the optimal method for monitoring treatment with metastatic breast cancer?

Therefore, the implementation of sensitive tests to monitor disease progression is crucial. Imaging studies are routinely used to evaluate treatment response of metastatic disease after initial confirmation of metastasis by pathologic assessment. However, imaging studies fall short of detecting minimal or evolving disease. Even the functional imaging modalities such as positron-emission tomography (PET) can detect metastatic disease only when it is larger than several millimeters in diameter. Although PET scan is shown to be more sensitive than conventional imaging (ie, computed tomography [CT] and magnetic resonance imaging [MRI]) in the detection of metastatic and recurrent disease, there is no compelling evidence to suggest a benefit in predicting treatment response in these patients.[2] Thus, the development of sensitive biologic marker tests has long been desirable, and remains a constant dilemma in clinical practice.

Serologic Markers Used in Breast Cancer

THE OPTIONS

• Measurement of MUC1 serologic tumor markers (CA 15-3 and CA 27.29)
• Measurement of carcinoembryonic antigen
• Clinical assessment and radiologic imaging
• Circulating tumor cell (CTC) testing

Serial measurement of tumor markers after primary treatment for breast cancer can detect preclinical recurrent disease with lead times of about 2 to 9 months. But the clinical significance of this finding is unknown.[3] In 1996, an American Society of Clinical Oncology (ASCO) expert panel recommended that a five- to tenfold increase of CA 15-3 above the normal limit be considered an alert for the presence of metastatic disease.[4] However, the assay lacks sensitivity and specificity, and increased levels of this antigen can be seen in individuals with no breast cancer.[4] The following serologic markers are frequently used in current practice to monitor disease status of patients with breast cancer.
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- CA 15-3
- CA 27.29
- Carcinoembryonic antigen (CEA)
- HER2 extracellular domain (ECD)

ASCO recently updated its guidelines for the use of tumor markers in breast cancer.[5] The ASCO panel recognized CA 15-3, CA 27.29, and CEA to be of clinical utility in breast cancer management. A literature review of the utility of serum tumor markers in breast cancer has been published elsewhere.[3]

Both CA 15-3 and CA 27.29 received US Food and Drug Administration (FDA) approval in 1996 to be used in surveillance for disease recurrence or metastasis in patients with stage II/III breast cancer.[6,7]

MUC1 Markers

Both commonly used tumor markers of breast cancer—CA 15.3 and CA 27.29—measure the product of the MUC1 gene. This gene codes for a very heterogeneous large (300–400 kD) mucin glycoprotein, also called polymorphic epithelial mucin (PEM), which is expressed in most glandular epithelial cells.[8] Tumors involving glandular organs (eg, breast cancer) sometimes overexpress this mucin glycoprotein. Excess mucin is subsequently shed into the circulation, making serum assays useful as tumor markers.[9] In spite of the presence of multiple assays that can measure the MUC1 glycoprotein in serum, only two assays are used in clinical practice—CA 15-3 and CA 27.29. Data comparing 10 commercial assay methods for these two markers have shown a strong correlation among these tests.[10]

One study compared CA 27.29 levels with those of urinary deoxypyridinoline (DPD [a bone resorption marker]), serum calcium, and alkaline phosphatase (ALP) in breast cancer patients with and without bone metastases. The best correlation with metastatic disease was achieved with CA 27.29.[11]

Another study compared CA 27.29 and CA 15-3 in 603 patients with breast cancer and 194 healthy controls. It showed excellent correlation between high marker levels and breast cancer, with CA 27.29 achieving the highest significance level.[12] High preoperative levels of CA 15-3 were shown to be associated with an adverse patient outcome.[13,14]

Carcinoembryonic Antigen

The CEA test for MBC is less sensitive compared to the MUC1 assays. CEA can be elevated in up to 60% of patients with metastatic disease, compared with about 80% who have elevated levels of the MUC1 antigen.[15] CEA testing does not have an additive impact when used with MUC1 levels. A study of 53 patients with MBC showed that CA 15-3 and CEA levels were elevated in 94% and 69%, respectively, and CEA was elevated in only one patient with a normal CA 15-3 level.[16] A study suggested that CA 27.29 is more sensitive and specific than CEA.[17]

The ASCO management guidelines for breast cancer recommend against obtaining serum tumor markers (CA 15-3, CA 27.29, or CEA) during routine surveillance after adjuvant setting.[18] However, when treating patients with MBC, changes in these marker levels are assumed to reflect disease progression or response to therapy, albeit with low sensitivity and specificity. The ASCO guidelines for using tumor markers in breast cancer, published in 2007, suggest the use of MUC1 and CEA assays initially in patients with metastatic disease, but discourage continued measurement if the MUC1 assay is elevated. When the CEA level is used for follow-up of metastatic disease, it should be noted that this measurement may spurious rise during the first 4 to 6 weeks of a new therapy.[5]

HER2 Extracellular Domain

Serum concentrations of the shed form of HER2 have also been widely investigated for potential prognostic value in breast cancer. A published systematic review of the literature evaluated the correlation between serum level of HER2 ECD and clinical outcome in studies that involved > 6,500 patients with breast cancer. Increased ECD predicted a poor response to hormonal therapy but predicted a good response to trastuzumab (Herceptin).[19] The analysis did not explicitly identify the ECD concentration as an independent prognostic factor. The lack of either high-quality studies or consistent results prompted the ASCO guidelines panel to exclude this test in any clinical setting of breast cancer management.[5]

Circulating Tumor Cell Test

Epithelial tumor cells have been shown to be shed from breast cancer tumors into circulation.[20]
Indeed, the prognostic significance of the circulating tumor cell (CTC) test in patients with breast cancer was first questioned more than 40 years ago.[21,22] A validated methodology has recently been developed to measure the level of CTCs in the peripheral blood of patients with MBC.[23] Many clinical studies have been performed to evaluate the utility of the CTC test in breast cancer. Table 1 lists studies that will be discussed in this article.

<table>
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<td>Clinical Studies of CTC Testing in Breast Cancer</td>
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<td>Number of MBC patients</td>
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<td>Metastatic Breast Cancer</td>
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<td>Cristofanilli et al, 2004[25]</td>
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<td>Cristofanilli et al, 2005[27]</td>
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<td>Hayes et al, 2006[26]</td>
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<td>Yie et al, 2006[29]</td>
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<td>Mueller, 2007[34]</td>
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<tr>
<td>Adjuvant Studies</td>
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<td>Rack et al, 2007[36]</td>
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CTC = circulating tumor cell; MBC = metastatic breast cancer.

- **Method of Isolation of CTC**—The US Food and Drug Administration (FDA) cleared the CellSearch assay (Veridex, Warren, NJ) for detection of CTCs. The system uses the CellSearch Epithelial Cell Kit. The procedure entails adding antibody-coated magnetic beads to the blood sample to distinguish cells using fluorescently labeled monoclonal antibodies against the epithelial-cell adhesion molecule.[24]

- **Clinical Trials of CTC Testing in MBC**—A prospective multicenter study tested 177 patients with MBC for the number of CTCs before and after a new line of treatment. Imaging studies were evaluated blindly to define disease status. Disease evaluation continued thereafter every 9 to 12 weeks. The control group comprised healthy women and women with benign breast diseases. The study showed that MBC patients with a baseline (before starting treatment) CTC level ≥ 5 (per 7.5 mL of whole blood) had a shorter median progression-free survival (2.7 vs 7.0 months, \( P < .001 \)) and shorter overall survival (10.1 vs > 18 months, \( P < .001 \)). This difference in survival remained significant when posttreatment CTC levels were evaluated as well. Multivariate analysis showed that, of all the variables, the levels of CTC both at baseline and after treatment were the most significant predictors of progression-free and overall survival.[25] A follow-up analysis of the same study showed that serial estimation of CTC level up to 20 weeks correlates with progression-free and overall survival.[26] This suggests that elevated CTC level at any time during therapy can reflect disease progression and mortality risk for MBC patients. Another
subset analysis was done on 83 (of the 177) patients who were receiving first-line treatment for metastatic disease. CTC level was assessed in these patients at baseline and monthly thereafter for up to 6 months, for a median follow-up of 12.2 months. CTC levels before and after starting therapy were strongly associated with various parameters of both the CA 27.29 test and CTC test in different patients. This same series of 177 patients from the investigation by Cristofanilli and colleagues[25] were evaluated in a study of the correlation between MUC1 protein (CA 27.29 and/or CA 15-3) and CTC in 65 patients who underwent both tests at serial time points. The study showed that 37% of patients had ≥ 5 CTCs, while 29% had more than a 25% increase in MUC1 at first follow-up. CTC levels and change in MUC1 did not significantly correlate at any time. Although both change in MUC1 and CTC level correlated with progression-free survival, only CTC level correlated with overall survival (P = .006).[31]

Another study has compared CTC levels with the serum marker CA 27.29 in a community-based practice.[32] A total of 50 patients with MBC were evaluated for both CTC and CA 27.29 at baseline and monthly for 6 months. CTC was detected in 54% of patients with MBC, compared with 70% in the Cristofanilli et al study.[25] In the community-based study, CTC testing demonstrated high specificity (89%) and less sensitivity (70%) to detect disease progression shown by radiologic tests. Conversely, the traditional biomarker CA 27.29 had a higher sensitivity of 85% but was less specific (31%). Patients with < 5 CTCs at 1 month after starting treatment had a longer median progression-free survival (P = .023). CA 27.29 level failed to show a similar difference. The authors of this study suggested that in contrast to CA 27.29, high levels of CTCs could be reflecting tumor biology rather than tumor burden.[32]

A limited retrospective analysis showed a statistically significant correlation among PET/CT scan, tumor marker CA 27.29, and CTC test in MBC.[33] However, they still found an unexplained discordance of these test results. That is, the same result of the PET/CT scan was occasionally associated with various parameters of both the CA 27.29 test and CTC test in different patients. This discordance could again be reflecting the diverse tumor biology of MBC.

• CTCs With Neoadjuvant Treatment of Breast Cancer—A German study evaluated CTC testing in the neoadjuvant setting. CTC level was measured prior to starting systemic therapy in 245 patients with locally advanced breast cancer and after treatment of 67 patients. At least 1 CTC was detected in 22% of patients before starting treatment. CTCs were detected in only 10.4% of patients after treatment. CTC levels before and after systemic treatment were compared in 43 patients. In this study, 10 (23%) of 43 patients had detectable CTC levels before starting treatment and a negative CTC test after finishing treatment; 6 patients (14%) developed detectable CTC levels posttreatment, after having had no CTCs before treatment; and 27 patients (63%) were CTC-negative at both time points.[34]

This study shows that CTC can be detected in non-MBC patients at primary diagnosis and also after primary systemic treatment of locally advanced disease. To date, the study has reported neither survival analysis nor clinical outcome of these patients. These would be appealing goals for prospective clinical trials.

Another study was done to monitor the reduction of CTC during the first three to four cycles of neoadjuvant therapy in 30 locally advanced breast cancer patients. When the entire neoadjuvant regimen consisted of chemotherapy, the reduction in CTC level accurately predicted the final tumor size at surgery.[35]

• CTCs With Adjuvant Treatment of Breast Cancer—Another study evaluated CTC level at the time of primary diagnosis and during adjuvant therapy in 1,767 node-positive breast cancer patients. Follow-up CTC levels were assessed in 852 of these patients. In this study, 10% of patients had more than one CTC before the start of systemic treatment. The presence of CTCs did not correlate with tumor size (P = .07), grading (P = .30), hormonal status (P = .54), or HER2 status of the primary tumor (P = .26). However, CTC level was found to significantly correlate with the presence of lymph
node metastases ($P = .02$). None of 24 healthy control individuals showed > 1 CTC. Among the 852 patients with follow-up CTC tests after the completion of treatment, 11% were CTC-positive before starting systemic treatment, while 7% had > 1 CTC after completion of treatment. Among initially CTC-positive patients, 10% remained positive and 90% had a negative CTC test after chemotherapy. Of initially CTC-negative patients, 93% remained negative, whereas 7% had a positive CTC test ($P = .24$).[36] The study shows that patients with early breast cancer could have detectable CTCs in the absence of systemic metastases. The significance of persistent CTC levels after the completion of primary treatment remains undetermined, as the study did not provide survival or outcome analysis.

**Recommendations**

The following recommendations are based on interpretation of the available clinical trials (Table 2). A reasonable treatment algorithm for using CTCs in clinical practice was also published elsewhere.[32] Of note, the ASCO guidelines for using tumor markers in breast cancer recommended that the CTC test should not be used to make a diagnosis of breast cancer and that it should not influence treatment decisions in patients with MBC.

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**Table 2**

**Guidelines for Using CTC Measurement in Management of Metastatic Breast Cancer**

<table>
<thead>
<tr>
<th>Baseline CTC level:</th>
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<tr>
<td>If &lt; 5: Better outcome is anticipated; serial measurements may provide more reliable information</td>
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<tr>
<td>If ≥ 5: Worse outcome is anticipated; serial measurements may suggest response to treatment</td>
</tr>
</tbody>
</table>

**First follow-up CTC level (after 1 or 2 cycles):**

| If < 5: May imply response to treatment if level previously high; better outcome is anticipated |
| If ≥ 5: May imply poor response to treatment; worse outcome is anticipated |

Changing treatment is not recommended unless there is compelling evidence of clinical or radiologic disease progression. Results of the current intergroup study are awaited.

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Serologic tumor markers (CA 15-3 and CA 27.29) continue to aid in assessment of disease status in MBC patients, particularly when metastatic disease is not measurable or in cases of equivocal radiologic results (see Case Example on page 729).

Patients starting a new line of therapy for MBC may have an initial CTC test to predict their prognosis. CTC level may again be measured after one or two cycles of treatment. Unfavorable CTC levels imply a poor prognosis. Changes in the CTC level appear to precede radiologic changes, which are known to occur only after several weeks or months of therapy. However, it may be prudent to wait at least two cycles before changing treatment.[32] Moreover, since hormonal therapy works more slowly than chemotherapy, the optimal time for CTC evaluation may be 6 to 8 weeks after...
starting treatment in patients receiving hormonal therapy, but 3 to 5 weeks for those given chemotherapy.[27]
On the other hand, if CTC level is favorable (< 5), this may imply a good response to treatment.
Nevertheless, this finding must be interpreted with extreme caution because of the lower sensitivity
of the CTC test. Radiologic disease progression should not be ignored on the basis of a favorable CTC
level. However, a favorable CTC level with overt radiologic progression may still suggest a better
outcome.[30]

Controversies

RECOMMENDATIONS

• CA 15-3 and CA 27.29 continue to aid assessment of disease status in MBC patients
• Patients starting a new line of therapy for MBC may have an initial CTC test to predict prognosis.
• CTC level may again be measured after 1 or 2 cycles of treatment—6 to 8 weeks after starting
hormonal therapy or 3 to 5 weeks after starting chemotherapy. Unfavorable CTC levels (≥ 5 cells/7.5
mL of blood) imply a poor prognosis. A favorable CTC level (< 5) must be interpreted with caution.
Note: ASCO guidelines recommend against the CTC test to diagnose breast cancer or in treatment
decisions for patients with MBC.

The use of the MUC1 serologic tumor markers (CA 15-3 and CA 27.29) and CEA for routine
surveillance in early breast cancer is controversial. The European Group on Tumor Markers
recommends their use if detection of recurrent or metastatic disease would alter clinical
management.[37] If an asymptomatic patient with early breast cancer (particularly a patient with
high-risk features) develops rising serologic markers, this may warrant further close follow-up or
radiologic imaging. The impact of lead time for diagnosing metastatic disease by tumor markers on
clinical outcome has not been determined, especially with novel treatment options.

Despite these limitations, these tumor markers are widely used by oncologists for routine
surveillance of early breast cancer. About 5% of normal individuals may have a high serum marker
measurement. Physicians should be conversant with the causes of elevated tumor markers other
than breast cancer such as benign breast disease, liver diseases, and other malignancies,[38] as
summarized in Table 3.

Table 3

<table>
<thead>
<tr>
<th>Conditions Other Than Breast Cancer Associated With Elevated CA 27.29 Levels*</th>
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<tbody>
<tr>
<td>Benign breast diseases</td>
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<td>Ovarian cysts</td>
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<td>Liver diseases</td>
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<td>Other malignancies</td>
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<tr>
<td>• Gastric cancer</td>
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<td>• Colon cancer</td>
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<tr>
<td>• Pancreatic cancer</td>
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<td>• Ovarian cancer</td>
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*CA 27.29 levels may also be elevated in normal individuals.

It has been suggested that patients with a CTC level
below the clinical cutoff of 5 cells and even those with a CTC level of 0 may have an indolent form of
MBC.[39] Clinical trials are warranted to determine the clinical significance of routine surveillance of
the CTC level in breast cancer patients (particularly those at high risk) after adjuvant treatment.
The clinical utility of using the CTC test to change treatment for patients with MBC (or to opt for a
more aggressive first-line therapy) is not yet determined. The Breast Cancer Intergroup of North
America (Southwest Oncology Group [SWOG] and Cancer and Leukemia Group B [CALGB]) is
currently conducting a phase III randomized clinical trial (S-0500) to test the survival benefit of
changing treatment regimens based on CTC levels in women with MBC while they are undergoing
chemotherapy.
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