Elevation of serum CEA and CA15-3 levels during antitumor therapy predicts poor therapeutic response in advanced breast cancer patients

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Abstract. The aim of the present study was to assess the correlation between therapeutic response and carcinoembryonic antigen (CEA) and carbohydrate antigen 15-3 (CA15-3) levels in advanced breast cancer patients with non-assessable lesions or stable disease (SD) according to the Response Evaluation Criteria in Solid Tumors. A total of 232 female patients with recurrent tumors following radical mastectomy were recruited, including 76 patients with non-assessable lesions and 60 patients with SD. The correlation between CEA and CA15-3 changes, progression-free survival (PFS) and therapeutic response were analyzed in the non-assessable and SD patient groups. For all subjects, the association between the patients’ serum tumor markers levels and the clinical presentation of the tumor, as well as the correlation between initial tumor marker levels and PFS, were analyzed. An increase in CEA (an increment of >2 ng/ml) or CA15-3 levels (an increase of >15 U/ml) following the second cycle of treatment correlated with shorter PFS in both non-assessable and SD patients, and with poor clinical outcome in SD patients. High CA15-3 levels correlated with hormone receptor-positive tumors, multiple metastases and liver metastases. Bone metastases correlated with high levels of both CEA and CA15-3. Relatively low CEA and CA15-3 concentrations were associated with triple-negative and locally invasive tumors. High CEA and CA15-3 levels at the beginning of relapse correlated with shorter PFS. The present study illustrates that CEA and CA15-3 levels correlate with several factors in recurrent breast cancer patients. Elevated levels of CEA and CA15-3 at the beginning of relapse may predict shorter PFS. Furthermore, elevation of CEA and CA15-3 levels following the second therapeutic cycle predict poor therapeutic response in patients with non-assessable lesions and SD. Our findings suggest that alterations in CEA and CA15-3 levels can predict therapeutic response in advanced breast cancer patients.

Introduction

Breast cancer is the most frequent form of malignant cancer in women worldwide (1). While the primary tumor is often treatable, tumor recurrence remains the most frequent cause of breast cancer mortality. Thus, the treatment of metastatic disease is crucial for improving breast cancer survival (2). Furthermore, designing subsequent treatment strategies using accurate initial response data could improve the outcome of advanced breast cancer and reduce the use of ineffective chemotherapeutic agents (3).

One of the most popular criteria used to evaluate therapeutic strategies is referred to as Response Evaluation Criteria in Solid Tumors (RECIST) (4). According to RECIST 1.1, a patient’s therapeutic response can be classified into four conditions: Complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). In SD patients receiving chemotherapy, certain patients would develop PD over time, while other patients would maintain SD or even experience remission.
Previous evidence indicates that there are a number of meta-
static forms of breast cancer that are not adequately assessed by
RECISt (4), including pleural/pericardial effusion, ascites, the
majority of bone metastases and lesions resected by surgery.
In particular, ~50% of breast cancer patients develop bone
metastases (5), and a large number of these patients would be
non-assessable by RECISt. Various alternative methods have
been proposed to assess the therapeutic response of bone
metastases, including 18F-fluorodeoxyglucose–positron emis-
sion tomography (6) and bone-specific biochemical markers
such as N-terminal telopeptide (7,8). However, these indicators
are not applicable to other non-assessable lesions.

Previous studies suggest that carcinoembryonic antigen
(CEA) and carbohydrate antigen 15-3 (CA15-3) are predic-
tive markers of radiological response in metastatic breast
cancer (9). Thus, these markers may be useful for monitoring
the therapeutic response of metastatic breast cancer patients.
Despite extensive study of CEA and CA15-3, their utility as
breast cancer markers remains unclear (10). The majority
of tumor markers are used for early diagnosis, determining
prognosis, monitoring therapeutic efficacy and follow-up
subsequent to therapy (11-16). However, CEA and CA15-3
are unsuitable for early detection due to their low expres-
sion and lack of sensitivity in breast cancer (11,17). While
CEA and CA15-3 have been used to assess the follow-up
of patients with breast cancer (18), their clinical value has not
been assessed (11).

Although tumor markers alone are insufficient to evaluate
therapeutic response (19), several studies suggest that tumor
marker levels correlate with treatment response (3,20-23). For example, Robertson et al (3) reported that changes in the
levels of tumor markers correlated with patients' therapeutic
response, as assessed by imaging methods (3). Furthermore,
reduction in CEA and CA15-3 levels predicted a positive
response to systemic therapy in metastatic breast cancer
patients (23). However, to date, no studies have assessed the
 correlation between CEA and CA15-3 levels and therapeutic
response in patients with non-assessable lesions or SD.

In order to assess the predictive efficacy of CEA and
CA15-3 in metastatic breast cancer, CEA and CA15-3 levels
were compared with radiological response in a group of
patients classified as non-assessable or SD by RECISt 1.1.
In addition, it was analyzed which factors are associated with
pre-treatment levels of CEA and CA15-3, including progres-
sion-free survival (PFS). The present study should clarify the
prognostic value of CEA and CA15-3 as tumor markers in
metastatic breast cancer.

Patients and methods

Patients. All data were retrospectively collected from
232 female breast cancer patients in the Affiliated Tumor
Hospital of Harbin Medical University (Harbin, China).
Patients were included in the study if they underwent radical
mastectomy but experienced subsequent tumor recurrence
or metastasis. Patients were excluded from the study if their
CEA or CA15-3 levels were not measured at the time of the
initial relapse or did not undergo therapeutic intervention.
Patients' age ranged from 25 to 76 years, and all patients
received first-line treatment between July 2001 and February
2013 along with systemic therapies, including chemotherapy,
trastuzumab, endocrine therapy and bisphosphonate treatment
for bone metastases.

From the 232 enrolled subjects, patients with ≥1 measur-
able lesion according to RECISt were grouped as assessable
patients, while those with lesions resected by surgery or
non-measurable lesions (pleural/pericardial effusion, ascites
and bone metastases) were grouped as non-assessable patients.
At the first-line therapeutic cycle, 60 individuals classified
with SD were selected to study the predictive value of CEA and
CA15-3 levels in evaluating the therapeutic response. Patients
classified as non-assessable by RECISt (76 patients) who had
available CEA and CA15-3 data were selected to study the
predictive value of the levels of these markers in assessing the
therapeutic response in patients with non-assessable lesions.

Determination of tumor markers. Serum CEA concentra-
tions were determined using an Enzyme Immunoassay kit
(Dinabot, Tokyo, Japan), while serum CA15-3 levels were
determined using a radioimmunoassay kit (Roche Diagnostics,
Indianapolis, IN, USA). A threshold of 0.5 ng/ml CEA and
0-25 U/ml CA15-3 was used to determine the "normal" levels
of the respective markers. Levels >5 ng/ml CEA or >25 U/ml
CA15-3 were considered elevated in patients.

Assessment. CEA and CA15-3 levels were determined within
1 week prior to the initiation of systemic therapy, and were
then evaluated every 3 weeks during the course of therapy.
Non-assessable patients and patients receiving chemotherapy
or trastuzumab therapy underwent radiological examination,
which was performed every 6 weeks during treatment.

To study the association between tumor markers levels and
PFS, all 232 patients were divided into two groups based on
their CEA and CA15-3 levels at the time of relapse (normal and
elevated). Patients were subsequently divided into two groups
based on the relative changes in CEA and CA15-3 levels at
the end of the second therapy cycle: An increased group (an
increment of >2 ng/ml CEA or 15 U/ml CA15-3 relative to
pre-treatment levels) and a non-increase group (an increment
of <2 ng/ml CEA or 15 U/ml CA15-3, or any decrease relative
to pre-treatment levels).

The therapeutic response in patients with assessable lesions
was classified using RECISt into four categories: CR, PR, SD
and PD. For the 60 individuals classified as SD, the clinical
therapeutic response following the second cycle of therapy was
classified as the final clinical response. Final clinical response
was divided into two categories: PD and disease controlled
(DC). DC was defined as the lack of PD following all chemo-
therapy cycles. For patients with non-assessable lesions, PD
was defined as the appearance at ≥1 new lesion and/or progres-
sion of the existing lesions. All the patients participated in
follow-up treatment and testing until May 2013. The median
follow-up time of the patients was 11.78 months. Recurrent
disease was confirmed by biopsy or, in cases of multiple
metastases, by radiological examination.

Statistical analysis. All statistical analysis were carried
out using SPSS 19.0 (IBM SPSS, Armonk, NY, USA).
Statistical analysis of the differences among patient groups
was performed using the t-test and Mann-Whitney U-test for
Table I. Correlation between patients’ characteristics and initial tumor marker levels at the first relapse (n=232).

<table>
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<th>n</th>
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<th>CA15-3 levels (U/ml)</th>
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<td>SE</td>
<td>P-value</td>
<td>Mean/median</td>
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<td>5.67</td>
<td>NS&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>7.80</td>
<td>NS&lt;sup&gt;a&lt;/sup&gt;</td>
<td>33.08</td>
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</table>
Results

The correlation between the clinical characteristics of all 232 enrolled breast cancer patients and the CEA and CA15-3 levels at the time of relapse was initially analyzed (Table I). In particular, it was observed that CA15-3 levels were highly correlated with hormone receptor (HR) status. Significantly higher levels of CA15-3 were detected in estrogen receptor (ER)-positive, progesterone receptor-positive and HR-positive groups (P<0.001, P=0.001 and P<0.001, respectively), whereas CEA did not appear to be correlated with any HR. While there was no correlation between human epidermal growth factor receptor-2 (HER-2) status and either CEA or CA15-3 levels, both markers were negatively correlated with triple-negative breast cancer (CEA, P=0.021; and CA15-3, P<0.001).

In addition, it was noticed that the serum levels of CEA and CA15-3 were highly correlated with the location and number of metastatic sites in breast cancer patients. In particular, patients with multiple metastases had significantly higher CA15-3 levels than patients with a single metastatic site (P<0.001). However, CEA concentration did not appear to be correlated with the number of metastases (P>0.05). Similarly, increased levels of CA15-3, but not of CEA, were observed in patients with liver metastases (P=0.009). It was observed that the serum levels of CEA and CA15-3 correlated with shorter PFS in advanced breast cancer patients (Fig. 1). Patients with elevated CEA had a median PFS time of 12.10 months, compared with a PFS time of 18.33 months in patients with normal levels (P=0.001). Similarly, patients with elevated CA15-3 levels had a median PFS time of 12.50 months compared with 18.53 months in patients with normal CA15-3 levels (P=0.001).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n</th>
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<th>CA15-3 levels (U/ml)</th>
</tr>
</thead>
<tbody>
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<td></td>
<td></td>
<td>Mean/median</td>
<td>SE</td>
</tr>
<tr>
<td>Sites of metastases</td>
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<td>4.22</td>
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</table>

aMann-Whitney U-test was used for statistical calculations. bSamples were analyzed using a Student's t-test. cEither ER- or PR-positive. dBoth ER- and PR-negative. NS, not significant; BMI, body mass index; IDC, invasive ductal carcinoma; HR, hormone receptor; ER, estrogen receptor; PR, progesterone receptor; SE, standard error; HER-2, human epidermal growth factor receptor-2; CEA, carcinoembryonic antigen; CA15-3, carbohydrate antigen 15-3.
CEA and CA15-3 levels following the second therapy cycle were also predictors of PFS in breast cancer patients with non-assessable lesions. Patients with increased CEA levels (an increment of >2 ng/ml relative to pre-treatment levels) had significantly shorter PFS than patients with no increased CEA levels subsequent to therapy (6.72 vs. 17.74 months, respectively; P<0.001). Similarly, patients with increased CA15-3 levels (an increment of >15 U/ml relative to pre-treatment levels) following therapy had shorter PFS than those with no increased CA15-3 levels (7.71 vs. 17.26 months, respectively; P<0.0001; Fig. 2).

To assess the predictive value of CEA and CA15-3 in patients with SD, the correlations between the serum levels of these markers, PFS and final clinical outcome were analyzed in 60 patients classified as SD by RECIST subsequent to the second treatment cycle. An increase in CEA or CA15-3 levels correlated with a significantly shorter PFS (Fig. 3).

Furthermore, this increase in CEA or CA15-3 levels was also negatively correlated with achievement of a CD state (Table II). These data indicate that, even in patients with SD, elevated CEA and CA15-3 levels correlate with a poor prognosis. Taken together, these data suggest that CEA and CA15-3 are predictive of PFS at both the early stages of relapse and throughout the treatment, particularly in non-assessable patients and in those with SD.

Discussion

Predicting a patient's therapeutic response is critical to avoid side effects from unnecessary and ineffective drugs. Few studies have analyzed predictive factors for therapeutic response in advanced breast cancer patients classified as SD by RECIST or in patients with lesions that are not-assessable by RECIST. A major reason for this is that the therapeutic
response of such non-assessable lesions (e.g. ascites) cannot be adequately measured by radiological methods (4). In such cases, PFS is the only criteria to assess the therapeutic response in patients, making difficult to predict the patient’s response during treatment.

Previously established models used to predict cancer patients' response to chemotherapy are complex and not applicable to patients with surgically resected lesions (24). Furthermore, due to the low sensitivity of the currently available imaging techniques, it is difficult to detect small changes in the tumor burden (25), particularly in patients with SD. Therefore, it is necessary to develop alternative methods to predict therapeutic results in patients with SD or non-assessable lesions.

CA15-3 (also known as mucin 1) is overexpressed in >90% of human breast cancers and in their subsequent metastases (26). CA15-3 promotes tumor invasion and metastasis through activation of the mitogen-activated protein kinase signaling pathway (26) and downregulation of E-cadherin (27). Thus, elevated levels of CA15-3 would predict a poor prognosis with an increased risk of metastasis (28). Consistent with this, CA15-3 levels were observed to negatively correlate with PFS (29). Similarly, CEA has also been observed to correlate with treatment response (21,23,25,30-32). These reports support the results of our study, suggesting that CEA and CA15-3 may be useful markers for predicting patient prognosis and therapeutic response.

Our data suggest that CEA and CA15-3 can predict PFS and final clinical outcome in patients with either SD or non-assessable lesions. An increase of >2 ng/ml CEA or >15 U/ml CA15-3 following the second therapeutic cycle predicted a shorter PFS. Furthermore, elevation of CEA and CA15-3 following the second cycle of chemotherapy correlated with a poor final clinical response in SD patients.

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To date, few studies have analyzed the predictive potential of CEA and CA15-3 in advanced breast cancer patients who are not assessable by RECIST and in those with SD. These patient populations require an alternative determination of therapeutic

Table II. Correlation analysis of CEA and CA15-3 levels and final clinical response in patients classified with stable disease following the second chemotherapy cycle.

<table>
<thead>
<tr>
<th>Changes in markers</th>
<th>PD(^a), n</th>
<th>DC(^b), n</th>
<th>P-value(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEA (ng/ml)</td>
<td></td>
<td></td>
<td>0.011</td>
</tr>
<tr>
<td>Increase of ≤2 or decrease</td>
<td>6</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td>Increase of &gt;2</td>
<td>4</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>CA15-3 (U/ml)</td>
<td></td>
<td></td>
<td>0.034</td>
</tr>
<tr>
<td>Increase of ≤15 or decrease</td>
<td>6</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>Increase of &gt;15</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

Final clinical response refers to the comprehensive clinical assessment of the therapeutic response of the patient to the chemotherapy cycles subsequent to the second chemotherapy cycle. *If a PD response was assessed following any chemotherapy cycle, the final response was considered to be PD. *Only if no PD was assessed following any chemotherapy cycle, the patient was classified as DC. *Fisher’s exact test was used for statistical calculations. PD, progressive disease; DC, disease controlled; CEA, carcinoembryonic antigen; CA15-3, carbohydrate antigen 15-3.

Figure 3. PFS according to the variations in CEA and CA15-3 levels following the second therapeutic cycle in the 60 patients with stable disease. Kaplan-Meier graphs indicating the percentage of patients with PFS based on the changes in (A) CEA and (B) CA15-3 levels following the second cycle of chemotherapy. PFS, progression-free survival; CEA, carcinoembryonic antigen; CA15-3, carbohydrate antigen 15-3.
response, as current imaging-based methods are not capable of accurately evaluating the therapeutic response of metastatic lesions (5). Monitoring the serum concentrations of CEA and CA15-3 provides a simple and cost-effective method to predict the therapeutic response of these patients, thus improving the design of therapeutic strategies and minimizing unnecessary side effects due to ineffective treatments.

In our study, serum CEA and CA15-3 concentrations were predictive of HR status, number of metastases and location of metastatic lesions. Specifically, CA15-3 was strongly associated with liver metastasis and the presence of multiple metastatic lesions, while both CEA and CA15-3 were associated with bone metastasis. By contrast, lower levels of CEA and CA15-3 were identified in patients with triple-negative tumors and with regional lymph node recurrence. In addition, lower CA15-3 levels were identified in patients with localized invasion. These results are consistent with previous studies that link CEA and CA15-3 levels with breast cancer prognosis (33,34). Taken together, these data indicate that elevated levels of CEA and CA15-3 may be predictive of increased tumor burden in breast cancer patients.

Elevated serum levels of CEA and CA15-3 prior to therapy predicted shorter PFS in our patient groups. While this finding is consistent with several reports (33-35), one study suggested that elevated CA15-3 concentrations correlated with longer overall breast cancer patient survival (36). This positive correlation between CA15-3 and survival could be explained by the association between CA15-3 levels and ER status observed in our study, as ER is commonly used to predict a better prognosis (37,38). A potential explanation for this discrepancy may be the relatively low ratio of HR-positive patients in the previous study compared with our study. It is possible that the predictive value of CEA and CA15-3 may be dependent on the HR status of breast cancer patients. Further research is required to better understand the role of CEA and CA15-3 in distinct breast cancer subtypes.

To conclude, our study demonstrates the utility of CEA and CA15-3 as markers predicting the therapeutic response of advanced breast cancer patients. These markers may be particularly useful in patients with non-assessable lesions or in those with SD, as defined by RECIST. Additionally, our data indicate that determining the serum concentrations of CEA and CA15-3 provides a simple yet robust method to predict a patient's therapeutic response. However, since our results are based on a retrospective analysis, other tumor markers such as HER-2, epidermal growth factor receptor or tissue polypeptide antigen (25,39-41) were not included in our analysis. Analyzing these markers in addition to CEA and CA15-3 could potentially provide even more accurate predictions of therapeutic response than those reported in the present study. In conclusion, the determination of CEA and CA15-3 levels can provide a powerful tool to complement RECIST in assessing and predicting the therapeutic response of advanced breast cancer patients.

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References


