Serum biomarkers in breast cancer

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Breast cancer remains one of the main causes of death for women in Western countries, with a lifetime risk of developing this malignancy of 12.2% and a lifetime risk of death of 3.6%. While the incidence of breast cancer has increased over the last 30–40 years, mortality has remained stable, probably reflecting the benefits of earlier diagnosis as well as improved treatment options. The initial treatment of localised primary breast cancer is intended to cure the condition, and usually includes surgery and/or radiotherapy. In recent years, the prognosis for patients with breast cancer has improved due to the use of adjuvant hormonal therapy and adjuvant chemotherapy. Rational administration of these expensive and frequently unpleasant treatments requires identification both of those patients with localised disease at most risk of recurrence, and those who have distant metastases or micro-metastases that are unlikely to respond to local therapies. Objective methods for assessing the response to treatment in patients receiving such therapies are therefore highly desirable.

Tumour markers

There are currently a large number of markers used in breast cancer management. These include the MUC-1 family of mucin glycoproteins (e.g. CA15.3, BR27.29, MCA, CA549), CEA, oncoproteins (HER-2/neu or C-erbB-2), milk proteins, glycolytic enzymes and cytokeratins (e.g. tissue polypeptide antigen (TPA), tissue polypeptide specific antigen (TPS)). Members of the MUC-1 family are the most widely used serum tumour markers in breast cancer, but as they have similar diagnostic sensitivities and specificities, use of more than one MUC-1 antigen is unlikely to confer any advantage [1]. CEA measurement can, however, provide additional complementary information. For this reason, the combination of one MUC-1 marker with CEA is recommended [1]. In this review we will evaluate the possible clinical utility of the most commonly used tumour markers in the different stages of breast cancer, particularly emphasising their clinical value.

Localised breast cancer: diagnosis

In patients with primary localised breast cancer (15–35% of all patients), the low sensitivity of tumour markers rules out their use for diagnostic purposes. Nevertheless, tumour marker determination may help in establishing patient staging. High levels of CA15.3 (e.g. >50 U/mL) and/or CEA (e.g. >20 ng/mL) in patients thought to have localised disease suggest the presence of unsuspected metastatic disease. Tumour marker levels are related to the most important prognostic factors: tumour size and nodal involvement. Significantly higher tumour marker serum levels are found in patients with larger tumours and in those with nodal involvement [2, 3].

Prognosis

The most commonly used prognostic factors in breast cancer are: the number or positive axillary lymph nodes, tumour size, lymphatic and vascular invasion, histological tumour type, c-erbB2 and sex steroid receptors. It is particularly important to establish a prognosis in patients whose outcome could be so favourable that adjuvant treatment is unnecessary. Univariate and multivariate analyses of data from patients whose pre-treatment serum levels were abnormal have shown that elevated levels of tumour markers can be prognostic for a shorter disease-free survival (DFS) and overall survival (OS) [2-5].

Early diagnosis of recurrence

About 40–50% of patients with breast cancer develop distant metastases within five years after radical primary treatment. Experimental studies have shown that there is an improved response to treatment when a smaller tumour mass is present (the observation on which the use of adjuvant treatment is based). In this respect, it therefore seems that early detection of metastatic disease is an essential requisite for successful therapy in breast cancer patients.

Several publications have shown that, in 40–55% of treated patients, an increase in the serum level of MUC-1 markers provides the first indication of recurrence, even before clinical or radiological indication (e.g. by chest X-ray, liver ultrasonography, bone scans) [6, 7]. Additional CEA measurement can increase the sensitivity in the early detection of recurrence obtained with CA15.3 by up to 5–25% of the patients with a lead-time of between 2 and 18 months (mean 5.2 months). The sensitivity of tumour markers for detecting recurrent disease is clearly related to the site of recurrence. CEA and CA15.3 are not useful in the early diagnosis of loco-regional recurrence (sensitivity <30%), with clinical examination being the best detection method for these sites. In contrast, abnormal CEA and CA15.3 serum levels are found in 40–60% and 50–75%, respectively, of patients with distant metastases. Serial determinations of markers are particularly sensitive for the early detection of bone (65%–75%) and liver metastases (85%–90%), and the use of markers in these situations may enable a decrease in the frequency of both isotope scans and radiological procedures. Chest X-rays should be carried out for detecting lung metastases as serum markers lack sensitivity for the lung [2, 6, 7, 8].

The specificity of markers for the detection of recurrence in the follow-up of patients with no clinical evidence of disease depends on the cut-off points that are used for each particular marker. With the usual cut-off for CEA and CA15.3, namely 5 ng/ml and 30 U/ml respectively, the specificity ranges from 92–97%. The specificity can, however, be increased to almost 100% if higher cut-off values are used (10 ng/ml for CEA and 60 U/ml for CA15.3) and then there are two consecutive increases of more than 15% [6, 8].

The early detection of metastases has two different uses, one being the establishment of diagnosis and the second being the possibility of initiating systemic treatment earlier. However, despite the ability of markers to detect recurrent disease pre-clinically, the long-term benefits of such early detection in terms of response to therapy and patient survival remain to be defined [2].

Advanced disease: diagnosis

CA15.3 is the most sensitive tumour marker in breast cancer (55–70%), but its sensitivity is insufficient for it to be used alone. Most reports indicate that by using CEA as well as CA15.3, it is possible to increase the sensitivity by 7% to 20% compared to that obtained with CA15.3 alone. Other tumour markers, such as cytokeratins or HER-2/neu, have been proposed as complements to CEA and/or CA15.3 to increase the sensitivity even higher, to at least 90%, in patients with distant metastases [9-11]. Tumour marker sensitivity in patients with advanced disease is significantly higher than in loco-regional disease and clearly related to the site of recurrence. The lowest tumour marker concentrations are found in patients with loco-regional recurrence and the highest in patients with metastases, particularly in those patients with liver metastases.

Disease monitoring

The main clinical application of tumour markers in advanced disease is in therapy monitoring. In contrast to tissue markers, blood tumour markers reflect a dynamic situation and have the advantage that their measurements can be repeated easily as often as required. Patients in remission usually show a serial decrease in the levels of markers, whereas patients with progressive disease...
generally have increasing levels. The use of tumour markers to monitor the patient’s progress has been shown in a number of studies to be superior to monitoring by conventional UICC criteria [9-11]. Biochemical changes often precede clinical or radiological signs of response or progression, thus potentially enabling earlier treatment decisions to be made regarding continuation of effective therapy, discontinuation of ineffective therapy, change of therapy, or more effective palliation. It has been suggested that biochemical assessment may result in cost savings of at least 50% when compared with assessment by clinical or radiological criteria, since this latter approach often requires expensive imaging techniques, such as computer tomography (CT) scans [12]. To use tumour markers in therapy monitoring, they should be measured prior to every chemotherapy course and at least three monthly for patients receiving hormone therapy.

There is little agreement in the literature about what constitutes a clinically significant change in marker level. The European Group on Tumour Markers (EGTM) panel [2] considers an increase to be significant when the levels of tumour marker increase by at least 25% from the previous value, when this is out of the normal range. Such an increase should be confirmed in a second serum assay from a sample obtained within one month. If this shows a further increase, progressive disease is indicated. A decrease of more than 50% in the tumour marker serum levels indicates response. Certain treatment regimens may cause transient increases in serum marker levels, a phenomenon known as "spiking," thus any increases observed shortly after treatment must always be confirmed [13].

Measurement of serum markers

Analytical requirements for tumour markers are similar to those for most other clinical analytes: the correct and appropriate specimen should be analysed by a method that meets defined quality requirements for both Internal Quality Control (IQC) and External Quality Assessment (EQA). It is important to note, however, that tumour marker assay systems from different manufacturers can give significantly different results with the same serum. For this reason, any change of assay method that has to be introduced during serial patient monitoring should be carried out with considerable care. Likewise, interpretation of sequential measurements is a task for specialists who are able to integrate information at a multidisciplinary level in collaboration with general practitioners, surgeons and oncologists.

References


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