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Serum markers in breast cancer: are they of value and will they get better?

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Available serum markers for breast cancer include CA 15-3, BR 27.29 (also known as CA27.29), CEA, tissue polypeptide antigen (TPA), tissue polypeptide specific antigen (TPS) and the shed form of HER-2. Of these, the most widely used are CA 15-3 and CEA (for review, see refs 1, 2). The aim of this presentation is to discuss the present and likely future use of serum markers in breast cancer.

Screening/Aiding early diagnosis

Lack of sensitivity and specificity preclude the use of all existing serum markers for the early detection of breast cancer. Women with apparently localized breast

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cancer who present with a high preoperative marker level (e.g., 5-10 times the upper limit of normal) are likely to have advanced disease (3) and should undergo appropriate investigations to diagnose or exclude this possibility.

Determining prognosis

A number of studies have shown that elevated preoperative levels of either CA 15-3 or CEA are associated with poor outcome in patients with breast cancer (1). For example, in our study on 600 newly diagnosed breast cancer patients, the prognostic impact of preoperative CA 15-3 levels was independent of tumour size and lymph node status (4). Importantly, the prognostic value of CA 15-3 was also observed in lymph node-negative patients, the subgroup of breast cancer patients in which new prognostic factors are most urgently needed.

Compared to tissue prognostic factors, serum markers have a number of advantages. Firstly, unlike tumour tissue which requires either biopsy or surgery, blood can be obtained with minimal inconvenience. Secondly, automated, relatively cheap and standardized assays are available for serum markers. Thirdly, serum-based markers can be determined in patients with small tumours including those with *in situ* cancers. For tissue-based markers, especially if freshly-frozen tissue is necessary, patients with very small tumours cannot be assessed.

Surveillance following surgery

Following surgery for breast cancer, it is now common practice to follow-up patients on a regular basis with clinical examination, radiology and tumour marker determinations. This practice is based on the belief that the early detection of recurrent or metastatic disease improves the chance of cure or results in an improved survival. From a biological point of view, it might be expected that the early detection of recurrent disease followed by the initiation of therapy would improve outcome compared with starting therapy when recurrence/metastasis is clinically evident. There is however little evidence available to support this hypothesis.

Serial determinations of markers such as CA 15-3 and CEA have the potential to detect recurrent breast cancer in asymptomatic women with median lead-times of 4-5 months (1, 3). Since it is unclear whether knowing this lead-time enhances outcome, guidelines vary in their recommendations regarding the use of tumour markers in postoperative surveillance in breast cancer. For example, the American Society of Oncology, the European Society of Medical Oncology and the European Society of Mastology recommend that serum markers should not be used in the routine surveillance of patients following primary treatment for breast cancer (3, 5, 6, 7). In contrast, the European Group on Tumour Markers (EGTM) and the National Academy of Clinical Biochemistry (NACB) recommend the use of markers during follow-up (8, 9).

Monitoring therapy in advanced disease

Following the commencement of therapy for advanced disease, it is important to know as soon as possible if the patient is responding to the treatment. If the patient is benefiting, clearly treatment should be continued. If on the other hand, treatment is not effective, an alternative therapy might be given. If an alternative therapy is unavailable, these patients could be willing to participate in clinical trials or they could decide to avoid further therapy.

A convenient and relatively inexpensive approach for helping to establish response is by measuring serum markers such as CA 15-3 or CEA. Generally, decreasing marker levels correlate with tumour response while increasing markers levels correlate with tumour regression (10-12). According to the EGTM guidelines (8), markers should be measured prior to every chemotherapy course and at least three monthly intervals for patients receiving hormone therapy. The

EGTM defines an increase in marker concentration of at least 25% to be significant (8). It is recommended that such an increase be confirmed with a second specimen obtained within a month. If the increase is confirmed, this provides evidence of progressive disease. Similarly, a confirmed decrease in serum levels of more than 50% was stated to be consistent with tumour regression (8).

In contrast to the EGTM recommendations, the ASCO guidelines state that neither CA 15-3 nor CEA should be routinely used for monitoring therapy in patients with advanced breast cancer (17, 23). However, this panel also stated "that in exceptional circumstances such as the presence of osseous metastasis, which are difficult to evaluate clinically, the marker level may be able to support the clinical estimate of disease status. However, the marker cannot in any situation stand alone to define response to treatment" (3, 6).

The European Society of Mastology (EUSOMA) also recommend against the general use of serum markers for monitoring therapy in advanced breast cancer (7). However, as with the ASCO guidelines, the EUSOMA guidelines stated that "in the absence of evaluable disease, increase in tumour marker accompanied by an increase in symptoms (e.g., bone pain) should be taken as indicating disease progression". Also, according to these guidelines, "an increase in serum markers without symptoms of progression should prompt a complete work-up to investigate for progression of known disease sites or appearance of new sites" (7).

Potential new markers for breast cancer

A desirable property of a serum marker is organ-specificity. None of the available serum markers for breast cancer is breast-specific as all can be elevated in serum from patients with most types of adenocarcinoma, especially in patients with advanced disease (1).

In recent years however, a number of proteins have been described that are expressed almost exclusively in breast tissue including breast cancer. These include, mammaglobin A (10-13), lipophilin B (14-15), NY-BR-1 (16,17), B726P (18), and small breast epithelial mucin (SBEM) (19). The challenge now is to devise sensitive and specific assays for measuring these proteins in serum and then evaluate their clinical value in breast cancer.

Will serum markers for breast cancer get better?

As mentioned above, the main problem with all existing serum markers for breast cancer is lack of sensitivity for early disease and lack of specificity for breast cancer. Clearly, new markers must offer improved sensitivity and specificity. One of the most promising approaches in this respect is the use of proteomics. In recent years a number of preliminary reports claimed to be able to detect breast cancer with sensitivities and specificities of 85-95% (for review, see ref.. 20). These findings however, will require extensive validation before they can be used clinically. Finally, if the relatively breast-

specific proteins mentioned above could be detected in serum, they also have the potential to provide a new generation of serum markers for breast cancer.

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Diagnosis and treatment of thyroid cancer: a view from the Dutch consensus

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Thyroid cancer is a rare cancer, with an incidence of 1/100,000 in men and 3/100,000 in women. This results in about 350 new patients every year in the Netherlands.

For the overall survival is good, the prevalence is relatively high 1/4000, resulting in about 4000 patients in the Netherlands (1). Histologically several subtypes of malignant thyroid tumours can be distinguished: the differentiated (papillary, follicular and Hürthle)

carcinoma originating from the follicular epithelium, the medullary carcinoma consisting of malignant transformed C cells, and the anaplastic carcinoma, often considered to represent the terminal stage in the dedifferentiation of a thyroid tumour.

Recently, it has been reported that the incidence of thyroid cancer has been increased with 2.4 fold in the United States, but the overall mortality has been remained stable. This increase is attributable to the increase of small papillary thyroid cancers, reflecting early detection or subclinical disease (2).

Treatment of thyroid cancer

Surgery is the cornerstone of treatment, When an uni-

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