

Tumor Markers in Breast Cancer – Evaluation of their Clinical Usefulness

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ABSTRACT

Breast cancer is the most common neoplasm affecting women in the Western world. Many studies are still conducted with the purpose of finding markers that could be used for early diagnosis and/or serve as possible reliable prognostic or predictive parameters, but with conflicting results. At present, no markers are available for an early diagnosis of breast cancer. For surveillance of patients with diagnosed breast cancer the most widely used serum markers are CA 15-3 and CEA which, in combination with other clinical parameters, could have clinical significance. The most useful and clinically important tissue-based markers in breast cancer are estrogen and progesterone receptors, used as a basis for hormonal therapy, and HER-2 receptors, essential in selecting patients for the treatment with Herceptin®. New or potentially new markers for breast cancer include BRCA1 and BRCA2 genes for selecting patients at high risk of developing hereditary breast cancer, as well as urokinase plasminogen activator and inhibitor for assessing prognosis in lymph node-negative patients. Results of tumor and patient genetic analyses including their clinical evaluation will enable application of more individualized and personalized approach in diagnosis and therapy of breast cancer patients.

Key words: breast cancer, serum tumor markers, tissue tumor markers, genetic tumor markers, clinical application

Introduction

Breast cancer is the most common type of non-skin cancer and one of the most common cause of cancer death for women in Western countries¹. About 1.2 million women will be diagnosed with breast cancer annually worldwide and about 411.000 will die from this disease². According to American Cancer Society 95% of new breast cancer cases and 97% of breast cancer deaths occur in women aged 40 and older³. Also, 50% of women who developed breast cancer are age 61 or younger at the time of diagnosis³. Lifetime risk of developing this malignancy is 12.2% and a lifetime risk of death is 3.6%^{4,5}. Multiple factors are associated with an increase in breast cancer risk, including genetic and familial predisposition, hormonal factors, diet, benign breast diseases and environmental factors^{5,6}. Over the past decade many improvements and new discoveries in the diagnosis, staging

and treatment of breast cancer patients, resulted in increased survival of breast cancer patients.

Breast cancer is a heterogeneous and progressive disease and its early detection remains one of the most urgent issues in cancer research. Because many breast cancers still escape early detection, identification of biological tumor markers able to reveal early stage disease may greatly reduce related mortality⁷. Furthermore, an effective follow-up is needed for all treated patients who may develop progression recurrence of the disease during their life⁸.

Potential use of markers in breast cancer include early diagnosis of the disease, determining prognosis, predicting response or resistance to specific therapies, surveillance after primary surgery and monitoring ther-

apy in patients with advanced disease⁹. Because tumor markers have weak sensitivity and specificity, especially in patients with early stage disease, their prognostic relevance and clinical usefulness is still controversial. So far, the main prognostic factors for both disease free survival (DFS) and overall survival (OS) in breast cancer patients are nodal involvement, tumor size, lymphatic and vascular invasion, histological grade, nuclear grade and sex steroid receptors^{5,6}.

Serum Tumor Markers

Serum tumor markers (STM) are soluble molecules in blood, usually glycoproteins, detected by monoclonal antibodies. They are released into the blood by tumor cells or by other cells in response to tumor cells. STM are the most extensively used in clinical practice because they reflect the dynamic evolution of the disease and their levels can be easily repeated when required⁹. STM are widely examined for detection of malignancies, for assessing outcome or predicting recurrence and for monitoring the response to anticancer therapies⁹.

Some of STM commonly used in breast cancer patients include certain members of MUC-1 family of mucin glycoproteins, such as CA 15-3 (PEM – polymorphic epithelial mucin; or EMA – epithelial membrane antigen; or episalin), CA 27.29, MCA and CA 549; carcinoembryonic antigen (CEA), certain oncoproteins (shed form of HER-2) and cytokeratins (TPA, TPS). Members of the MUC-1 family are most widely used STM in breast cancer, and among them CA 15-3 is generally regarded as the most specific and sensitive¹⁰. Because of their similar diagnostic sensitivities and specificities, the use of more than one MUC-1 marker is unlikely to confer any advantage¹¹. CA 15-3 and CEA are currently the most often used tumor markers for breast cancer in clinical practice¹².

MUC-1

MUC-1 is a high weight glycoprotein encoded by the MUC-1 gene and well expressed on the apical surface of most polarized epithelial cells of different organs including breast, stomach, pancreas, bladder and respiratory tract¹³. In normal breast tissue MUC-1 is expressed in the ducts and acini from where it is released into the milk in soluble form or bound to milk fat globules. Neoplastic transformation is associated with disruption of normal cell polarization and tissue architecture leading to MUC-1 shedding in the bloodstream where it can be measured by means of immunoassays. MUC-1 is biologically significant because it can activate membrane receptors for growth factors, reduce E-cadherin-mediated cell adhesion thereby promoting cell migration, and reduce the cellular apoptotic response to oxidative stress^{14–17}.

Members of MUC-1 family are detected by monoclonal antibodies that bind to epitopes on the MUC-1 molecule. Reactive with different epitopes monoclonal antibodies identified several serum antigens, such as cancer antigen CA 15-3, mucin-like carcinoma associated mucin (MCA), CA 549, CA 27.29, breast cancer mucin

(BCM), EMCA, M26 and M29¹⁸. Among these antigens, the most widely used is CA 15-3, and more recently CA 27.29. According some authors, CA 27.29 is similar to CA 15-3 for metastatic breast cancer detection and monitoring, but more sensitive¹⁸.

Carcinoembryonic antigen (CEA)

One of the first studied and used markers was carcinoembryonic antigen (CEA), an oncofetal glycoprotein that is expressed in normal mucosal cells and overexpressed by adenocarcinomas, primarily of the colon, rectum, breast, pancreas, and lung. Immunobiological and biochemical studies have revealed that CEA consists of a large family of at least 30 closely related cell surface glycoproteins encoded by about ten genes located on chromosome 19^{19,20}. The domain structure of CEA proteins and the gamma heavy chain of the immunoglobulin IgG are very similar, suggesting that CEA is part of the immunoglobulin gene »superfamily«. This finding indicates that CEA proteins may be involved in the intercellular or cellular-matrix recognition mechanisms.

Cytokeratins

Several widely used tumor markers such as tissue polypeptide antigen (TPA), tissue polypeptide specific antigen (TPS) and Cyfra 21.1 are molecules that structurally belong to the family of cytokeratins (CKs). CKs constitute one of the seven classes of intermediate filaments that, together with microtubules and actin microfilaments, make up the cytoskeleton of most eukaryotic cells^{21,22}. Human CKs comprise 20 related polypeptides (CKs 1–20) which, on the basis of sequence homologies, can be separated into two subfamilies. CKs 9–20 are the more acidic, type-I CKs, while CKs 1–8 form the neutral/basic type II group of proteins. In epithelial cells from many tissues, the combinations CK8/CK18 and CK8/CK19 are very often expressed. These pairs of CKs are also very commonly found in the vast majority of epithelial breast carcinomas^{23–25}. Different tumor marker assays measuring CK8, CK18 and CK19 fragments have been developed, the most widely used being TPA, TPS and Cyfra 21.1. The TPA test recognizes all three CKs (CK8, CK18 and CK19), TPS measures CK8 and CK18, and Cyfra 21.1 detects CK8 and CK19.

Assessment of serum tumor markers' clinical use

Screening and early diagnosis

Due to low sensitivity of available tumor markers in early stage disease, only mammographic screening may result in a justified suspicion of breast cancer²⁶. Various studies have demonstrated that the diagnostic sensitivity of the CA 15-3 test is about 10–15%, 20–25% and 30–45% in patients with stage I, stage II and stage III disease, respectively¹². However, low levels of tumor markers in patients with suspected breast cancer does not exclude the presence of malignancy¹¹.

The sensitivity and specificity of tumor markers is significantly higher in patients with advanced disease and it is related to the site of recurrence¹¹. Simultaneous use of CA 15-3 and CEA markers allows early diagnosis of metastases (mainly in bone and liver) in up to 60–80% of patients with breast cancer¹¹. By using combinations of CA 15-3, CEA and cytokeratins, it was possible to increase the sensitivity to at least 90% in patients with distant metastases¹¹. Recent reports indicate that CA 27.29 is a more sensitive test than CA 15-3²⁷. The CA 27.29 level is elevated in approximately one third of women with early-stage breast cancer (stage I or II) and in two thirds of women with late-stage disease (stage III or IV)²⁷. However, CA 27.29 lacks predictive value in the earliest stages of breast cancer and thus has no role in screening or diagnosing the malignancy.

Prognosis and surveillance

Various studies confirmed that preoperative elevated levels of either CA 15-3 or CEA are indicators of adverse effects in breast cancer patients, and therefore can be used as prognostic factors for both disease-free survival (DFS) and overall survival (OS)^{28,29}. Together with CA 15.3 and CEA, serum HER-2 concentrations with tissue overexpression showed to be useful tool in the prognostic evaluation of patients with primary breast cancer³⁰. There are still conflicting data for CA 15-3 marker but so far, it appeared to have the strongest prognostic value among STM. Elevated CA 15-3 level can be a marker of enhanced risk of recurrence and mortality in both early- and late stage breast cancer¹². Indeed, in some studies the prognostic impact of CA 15-3 was independent of tumor size and axillary nodal status^{31,32}. Significantly, in two reports^{31,32} CA 15-3 was found to be prognostic in lymph node-negative breast cancer patients. In another study however, CA 15-3 was not prognostic in patients free of axillary nodal metastases³³. Although some patients with high levels of CA15-3 demonstrated shorter DFS and OS, the role of this marker as independent prognostic factors has not been proven¹².

It has been shown that high preoperative concentrations of CEA can be associated with poor prognosis in breast cancer^{29,33}. Furthermore, in one large study (n = 1046) patients with a decrease of 33% between pre- and postoperative concentrations were found to have a worse outcome than those with a lesser decrease²⁹. In multivariate analysis, this decrease in CEA predicted outcome independent of tumor size, lymph node status, and progesterone receptors. Nevertheless, elevated CEA levels can suggest worse, unaffected or even better prognosis, therefore CEA determination is of limited clinical utility.

Therapy monitoring

Potential clinical application of STM in monitoring breast cancer patients response to therapy has been subject of numerous studies, but with controversial results⁷. For patients with metastatic breast cancer, some correlation to response to therapy was reported for CA 15-3, MCA, CA 549 and for TPS, but CA 15-3 shown to be more

effective and generally superior to CEA and other STM^{7,12}. According to meta-analysis, in a majority of patients treated for advanced breast cancer, decreasing level of CA 15-3 correlated with the response to therapy, while patients with cancer progression had increasing level of this marker⁷. CA 15-3 was shown to be useful in the monitoring of response to endocrine therapy and cytotoxic therapy¹².

For patients with advanced breast cancer International Unit against Cancer (UICC) criteria, referring to clinical characteristics of tumor burden, have been traditionally used for assessing response to therapy³⁴. Combination of CA 15-3, CEA and erythrocyte sedimentation rate (ESR) has been used to obtain biochemical score index that correlated with UICC criteria used for therapy monitoring¹¹. Changes in serial measurements of a MUC-1 may be helpful in assessing the course of the disease and some authors suggested a major role of CA 15-3 in monitoring the response to chemotherapy⁷. However, not all international guidelines recommend use of CA 15-3 in therapy monitoring, since up to one third of advanced breast cancer patients did not show any changes of tumor marker at disease progression⁷. In contrast to the American Society of Clinical Oncology (ASCO) Panel, both the National Academy of Clinical Biochemistry (NACB) and European Group of Tumor Markers (EGTM) Panels recommended use of CA 15-3 for monitoring therapy in patients with advanced breast cancer^{11,35}.

Emerging data suggest that determination of serum HER-2 may be of use in patients undergoing treatment with trastuzumab-based therapy. Preliminary findings suggest that high serum HER-2 concentrations are associated with both poor response to endocrine therapy and cyclophosphamide-methotrexate-5-fluorouracil-based chemotherapy but can predict an improved response to a combination of trastuzumab (Herceptin®) and chemotherapy³⁶. These early findings, however, require validation in a large prospective trial before serum HER-2 level can be recommended for monitoring of trastuzumab-based treatment in patients with advanced breast cancer.

Tissue Tumor Markers

Tissue tumor markers can be identified with different methods in tumor tissue and some of them can have prognostic and predictive value. Tissue markers are tissue antigens such as proteins or hormone receptors detected by antibodies that bind to tissue antigens in fresh, frozen or formalin-fixed, paraffin-embedded tissue sections. Tissue based markers are primarily measured in order to determine prognosis and predict response to therapy¹¹. At present, steroid receptors, estrogen (ER) and progesterone (PR) receptors, as well as HER-2 (also known as c-erbB-2 or neu) are markers accepted in standard clinical practice. They are not useful in early diagnosis, as they may be present in both benign and malignant tissue, but they have prognostic and predictive value in primary and in metastatic breast cancer. Clinical decisions regarding hormonal or immunotherapy in breast

cancer patients is based on obligatory determination of steroid and HER-2 receptors in all breast tumors.

Urokinase plasminogen activator (uPA) and plasminogen activator inhibitor 1 (PAI-1) represents potential markers for determining prognosis in lymph node-negative breast cancer patients¹¹.

Breast cancer, as heterogeneous disease, can be classified using gene microarray analyses into four different subtypes, which also include ER, PR and HER-2 receptor status. This classification includes: basal-like subtypes (which are mostly triple negative – ER negative, PR negative and HER2 negative), luminal A (ER positive and low grade), luminal B (ER positive and high grade) and HER2 positive. It has been shown that these breast cancer subtypes have different prognostic and possible therapeutic implications³⁷.

Estrogene and progesterone receptors

The ER has a central role in the development of breast cancer³⁸. According to the College of American Pathologists both the estrogene and the progesterone receptor constitute a first category of prognostic factors in breast cancer³⁹. ER and PR are transcriptional factors which mediate the actions of estrogens and progesterone, respectively^{40,41}. Both receptors are now known to exist in two different isoforms. For ER, these forms are known as ER- α and ER- β ⁴² and for PR the two forms are known as PRA and PRB⁴³. It appears that only ER- α is critical for mammary gland development and tumorigenesis. Existing assays for PR do not discriminate between the two forms.

Hormone status is considered a very strong predictor of response to hormonal therapy in breast cancer patients. In both early and advanced disease hormone receptor-positive patients have a significantly greater probability of responding to hormone therapy than patients lacking receptors⁴⁴. Therefore, hormone receptor determination is obligatory in all breast cancer patients and methodology of steroid receptor determination is recommended by ASCO guidelines. Three well-established assays exist for measuring hormone receptors, namely ligand binding, ELISA and immunohistochemistry¹¹. Positive hormone receptors represent basis for different hormonal therapy appliance in early stage, as well as advanced breast cancer disease.

Information on receptor status may also be of prognostic value. Generally, for the first 4–5 years after diagnosis, ER-positive patients have a better outcome than ER-negative patients⁴⁵. However, after this period, the favorable prognostic impact of ER is lost. Approximately 30–40% of ER positive patients do not respond to endocrine therapy, while some ER negative patients are responsive⁷. A further limitation of ER as a prognostic factor is that it is of little value in lymph node negative patients⁴⁵. However, hormone receptors may be combined with classic clinical prognostic factors in determining outcome in breast cancer patients¹¹.

HER-2 receptor

HER-2, a proto-oncogene, is the most commonly amplified oncogene in human breast cancer⁴⁶. HER-2 encodes a transmembrane protein belonging to the epidermal growth factor receptor family⁴⁷. HER-2 gene is either amplified or overexpressed in 15–30% of invasive breast cancers¹¹. Determination of HER-2 status is obligatory for all breast cancer patients. Methodology for identifying HER-2 status provided by ASCO recommendations includes immunohistochemistry, which measures over-expression of the HER-2 full-length oncoprotein (p185); fluorescent *in situ* hybridization (FISH), which measures the number of HER-2/neu gene copies⁴⁸. A third tissue method is chromogenic *in situ* hybridization (CISH)⁴⁹. Tumors with HER-2 overexpression tend to be higher grade and hormone receptor negative, resulting in a worse prognosis⁴⁵. Studies support that HER-2 overexpression is a poor prognostic factor, although its magnitude appears weak⁵⁰.

All patients with positive HER-2 receptors have to be treated by immunotherapy with Herceptin® (trastuzumab). To select breast cancer for the treatment with Herceptin® (trastuzumab), determination of HER-2 tumor expression is obligatory by all patients. Herceptin® is a humanized monoclonal antibody that binds with high affinity to the extracellular domain of HER-2, thereby blocking its role in signal transduction. Herceptin® is now widely used for the treatment of HER-2-positive tumor patients with advanced breast cancer, as well as for adjuvant treatment of HER-2 positive patients with early breast cancer. However, some HER-2 positive tumors have a primary or acquired resistance to trastuzumab. Patients with tumors that overexpress HER-2 appear to have relative resistance to some chemotherapy regimens, such as cyclophosphamide, methotrexate and 5-fluorouracil (CMF), but not to others, such as anthracycline-containing regimens⁵¹. The level of available evidence does not support using HER-2 status to predict response to chemotherapy⁵⁰.

Most published reports on axillary node-positive breast cancer patients conclude that either HER-2 gene amplification or overexpression correlates with an adverse outcome in patients with breast cancer⁵². HER-2 should not be used alone for determining outcome in patients with breast cancer.

uPA and PAI-1

Urokinase plasminogen activator (uPA) and its inhibitor PAI-1 have been investigated as potential prognostic markers in breast cancer patients. uPA is a serine protease implicated in cancer growth, invasion and metastasis⁵³. PAI-1 is an endogenous inhibitor of uPA but paradoxically is also involved in tumor progression. Multiple single institutional studies have shown that both uPA and PAI-1 are potent and independent prognostic factors in breast cancer. This prognostic impact of uPA and PAI-1 has been shown in both lymph node negative and lymph node-positive breast cancer patients⁵³. Patients with low levels of both these proteins are at a relatively

low risk of developing recurrent or metastatic disease and, consequently, may be able to avoid the toxic side effects and costs of adjuvant chemotherapy but further investigation is needed¹¹.

Other tissue-based markers

Potential biological breast cancer markers are subject of numerous investigations. One of the most common genetic alterations found in breast cancer is mutation of gene p53, which has a pivotal role in the entire mechanism of apoptosis⁵⁴. Although some studies showed intriguing results, the update of ASCO guidelines confirmed the lack of utility of p53 in management of breast cancer⁵⁵. Proliferation markers such as nucleic protein Ki-67 is also used as a marker for breast cancer, with maximal expression during S and M phase of cell cycle. Cathepsin D, a glycoprotein with proteolytic activity, associated with tumor growth and progression, has been found elevated in up to 69% of patients with metastatic breast cancer⁵⁵. Based on available evidence, a routine determinations of cathepsin D, or other breast cancer tissue markers such as cathepsin B, TGF- α , e-cadherin, nm23, or c-myc, cannot be recommended at present.

Gene expression profiling

Instead of measuring individual markers, the use of DNA microarray or gene expression profiling is a popular current research approach for determining prognosis or predict response to therapy. Although results are promising, this technology is technically demanding, time-consuming, expensive and requires further clinical evaluation.

Multigene expression: oncotype DXTM

Oncotype DXTM, created by Genomic Health, is a more recent example of new tumor marker development that has been included in the 2007 American Society of Clinical Oncology (ASCO) Clinical Guidelines on Use of Tumor Markers in Breast Cancer⁵⁵. It represents a diagnostic test that quantifies the likelihood of disease recurrence in women with early-stage breast cancer and assesses the likely benefit from certain types of chemotherapy. The investigators specifically developed the test to determine prognosis in ER-positive, lymph node-negative patients who were treated with tamoxifen⁵⁶.

Oncotype DXTM, also known as a genomic assay, is a noninvasive test performed on a small amount of the tissue that analyses the activation of a groups of genes from which can be established how a cancer is likely to grow and respond to treatment. During the test a panel of 21 genes is analyzed within a tumor with the use of RT-PCR, a highly reproducible laboratory assay that determines the expression of these genes. Based on this analysis Oncotype DXTM assigns the breast cancer a Recurrence Score (RS) that represents a number between 0 and 100 that corresponds to a specific likelihood of breast cancer recurrence within 10 years of the initial diagnosis. The lower your score the less likely the cancer is to recur and vice-versa.

Oncotype DXTM is both a prognostic test, since it provides more information about how likely (or unlikely) the breast cancer is to come back, and a predictive test, since it predicts the likelihood of benefit from chemotherapy treatment. 2007 ASCO Guidelines recommend the use of Oncotype DXTM to predict the risk of recurrence in patients treated with tamoxifen and to identify patients who are predicted to obtain the most therapeutic benefit from adjuvant tamoxifen and may not require adjuvant chemotherapy⁵⁵. Patients with high recurrence scores (RSs) appear to achieve relatively more benefit from adjuvant chemotherapy than from tamoxifen.

Besides Oncotype DXTM, there are three commercially available multigene assays to determine clinical outcomes in primary breast cancer: MammaPrint®, MapQuant DxTM and THEROS Breast Cancer Index^{TM57}. Among them, clinical use of Oncotype DXTM (21-gene RS assay) and MammaPrint® (70-gene assay) increased in recent years⁵⁷. Nevertheless, several limitations and caveats exist regarding the prediction utility of multigene assays and further clinical evaluation is needed⁵⁷.

Genetic Tumor Markers

BRCA1 and BRCA2

Genetic tumor markers BRCA1 and BRCA2 are a cancer predisposing human genes used for risk assessment in individuals with a familial history of breast cancer. They belong to a class of genes known as tumor suppressors which maintain genomic integrity to prevent dangerous genetic changes in normal cells. Inherited mutations can identify individuals who are at an increased risk for the development of breast and ovarian cancers, as well as other cancers. Although BRCA1 and BRCA2 mutations are strong predictors of breast cancer development, they occur in less than one out of 1000 women in breast cancer⁷. About 50 to 60% of women with hereditary mutation in BRCA1 and BRCA2 genes will develop breast cancer till the age of 70. Also, they can have enhanced risk of developing ovarian cancer⁷.

The BRCA1 gene is located on the long arm of chromosome 17 (17q21) and has 3.4 kb with 24 exons. It encodes a 190 kDa protein containing 1863 amino acids involved in regulating transcription, inhibiting cellular proliferation and repairing DNA^{58,59}. According to the biochemical analogy protein is homologue to granin protein family that is involved in suppression of epithelium proliferation of estrogen dependant tissue. Over 1000 mutations, mostly nonsense or frameshift, in the BRCA1 gene have now been described⁶⁰. BRCA2, larger gene than BRCA1, has 2.5 kb with 27 exons. It codes for a 380 kDa protein of 3418 amino acids with similar functions as BRCA1 protein, homologue to granin family⁶¹. The BRCA2 gene is located on chromosome 13q12⁶¹.

Studies showed that women who carry either a BRCA1 or BRCA2 gene mutations have 82% of lifetime risk of developing breast cancer⁶². BRCA1 mutation carriers have about 60% lifetime risk of ovarian cancer while BRCA2

mutation carriers have about 27%. Males possessing a mutation in BRCA2 gene have a 5% risk of developing breast cancer. BRCA1 mutation on the other hand, does not appear to increase the risk of male breast cancer⁶².

Genetic testing for BRCA1 or BRCA2 mutations in patients with a familial history of breast cancer may provide, along with other clinico-pathohistological parameters, information for patient-specific diagnostic and treatment regimens.

Recently, a lot of emphasis has been put on newly developed molecular approaches, genomics and especially proteomics, thanks to whom changes in molecular mechanisms and signaling pathways underlying breast cancer have been enlightened. Certain key genes including HOXA1, c-Myc, cyclin D1, and Bcl-2 that express oncolytic activity when altered, have been identified⁶³. Also, highly expressed BRMS1 gene can influence MHC genes that are directly involved in secretion, cell adhesion, proliferation, localization, and metabolism⁶³.

Conclusion

In order to obtain more successful diagnosis and therapy of breast cancer, finding markers for early diagnosis, reliable prognosis and therapy prediction could be of crucial importance. The clinical usefulness of tumor markers in breast cancer is still an area of investigation, with often controversial results. Due to low specificity and sensitivity, no markers are available at present for early diagnosis of breast cancer. For patients with diagnosed breast cancer, the most widely used serum markers are CA 15-3 and CEA, which in combination with other clinical parameters could have significance in patients' surveillance. Serial determination of these markers may be useful in routine therapy monitoring and for early detection of recurrence and progression during follow-up. The most useful and clinically important tissue-based mark-

ers in breast cancer are steroid receptors (estrogen and progesterone receptors) and HER-2 protooncogene receptor. Steroid receptor status is used to predict response to hormonal therapy, which represents an important form of treatment for patients with steroid receptors positive breast cancer. HER-2 protooncogene receptor has predictive value for response to immunotherapy and all patients with positive HER-2 receptors have to be treated with Herceptin® (trastuzumab), in both early and advanced breast cancer disease. Determination of steroid receptors and HER-2 receptor status is obligatory for all breast cancer patients. Genetic testing for BRCA1 or BRCA2 mutations in patients with a familial history of breast cancer may provide, along with other clinico-pathohistological parameters, information for patient-specific diagnostic and treatment regimens. uPA and PAI-1 are recently validated as prognostic factors for lymph node-negative breast cancer patients and thus may be used in selecting those node-negative patients who may not need to receive adjuvant chemotherapy. Genetic testing for BRCA1 or BRCA2 mutations in patients with a familial history of breast cancer may provide, along with other clinico-pathohistological parameters, information for patient-specific diagnostic and treatment regimens. Results of tumor and patient genetic analyses, including their clinical evaluation, will enable application of more individualized and personalized approach in diagnosis and therapy of breast cancer patients.

Human blood and tissue represent rich sources of biomarkers; therefore additional studies have to be conducted to discover new markers with the ultimate goal of exploiting their use in the screening and early diagnosis of primary breast cancer. The use of selected marker in breast cancer as prognostic or predictive parameters should lead to a better and a more cost effective management of these patients. Hopefully, this will result in enhanced survival and better quality of life of breast cancer patients.

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TUMORSKI MARKERI RAKA DOJKE – PROCJENA NJIHOVE KLINIČKE PRIMJENE

SAŽETAK

Rak dojke je najčešća maligna bolest žena u zapadnom svijetu. Mnoga istraživanja se još uvijek provode u cilju pronalazjenja markera koji bi mogli koristiti za rano dijagnostiku, te služiti kao mogući pouzdani prognostički ili prediktivni pokazatelji, međutim, rezultati tih istraživanja su kontradiktorni. Trenutno ne postoji marker za rano otkrivanje raka dojke. Za praćenje bolesnica s dijagnosticiranim rakom dojke, najčešće korišteni serumski markeri su CA 15-3 i CEA, koji u kombinaciji s drugim kliničkim pokazateljima mogu imati kliničku primjenu. Od tkivnih markera, najkorisniji i klinički najznačajniji markeri su estrogenski i progesteronski receptori, koji se koriste kao osnova hormonske terapije, te HER-2 receptori, ključni u odabiru bolesnika za liječenje Herceptinom®. Novi, ili potencijalno novi markeri raka dojke uključuju gene BRCA1 i BRCA2, koji se koriste u odabiru bolesnica s visokim rizikom razvoja nasljednog raka dojke, te urokinaza plazminogen aktivator i inhibitor, korišteni za procjenu prognoze u bolesnika s negativnim limfnim čvorovima. Rezultati genetičkih analiza tumora i bolesnica, uz njihovo kliničko vrednovanje, omogućit će individualizirani i personalizirani pristup dijagnostici i terapiji bolesnica s rakom dojke.