Journal of BUON **7**: 97-98, 2002
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EDITORIAL

Prognostic factors in breast cancer: do we really need the new ones?

In this issue of the J BUON Cianga et al. present their study over a possible prognostic role for p27 in breast cancer, a cell cycle regulating protein. The article deals with the p27 cdk-inhibitor in relation with some well-established breast cancer prognostic indices such as tumor size, regional lymph node involvement, steroid receptor positivity, as well as with the some of the "new generation" biomarkers (p53 and c-erbB-2 expression).

Classical prognostic parameters of breast cancer include patient's age and menopausal status and some tumor characteristics – tumor size (T), nodal status (N) and the presence of distant metastases (M) (TNM characteristics), as well as histological grade of the tumor [1,2]. Steroid receptor status can be added to these prognostic factors as a biologic characteristic that describes hormone-dependence of breast cancer and, hence, indirectly characterizing tumor aggressiveness [3]. Classical prognostic parameters allow a relatively reliable breast cancer staging. However, due to better organization of medical services, small breast cancers are more frequently detected nowadays as a result of screening programs. In these cases well-established prognostic parameters like tumor size are often useless and the most powerful prognosticator-regional lymph node involvement-is rare. However, breast cancer being a multistage disease also requires multiple new generation markers that may improve identification of biological aggressiveness, indicating also indirectly the most appropriate therapeutic approach. Briefly, indices that measure or are associated with biological processes involved in tumor progression can be examined as potential markers either in assessing prognosis or in predicting a therapeutic response.

The increasing knowledge about cell mechanisms involved in carcinogenesis directed the investigations towards variables characterizing cell proliferation and/or apoptosis, as well as cell cycle regulators [4-6]. Among them, growth factor receptors (EGF-R, c-erbB-2), cyclin-dependent kinase inhibitors (p21, p27), apoptotic regulators (p53, bcl-2) are in the narrow scope of the investigators' interest. According to the complexity of genetic pathways that can be altered by a particular gene aberration or incorrect regulation of gene expression, and also on protein level by interaction between encoded proteins, characterization of relevant "new generation" biomarkers is a very hard task that must be done with caution. Since a very large number of potential biomarkers is intensively studied, it is evident that a selection has to be made. Besides classical prognostic indices, the markers reflecting growth potential, invasive potential and tumor probability to respond to various anticancer therapies must be included.

The question whether we need new prognostic indices for breast cancer concerns mostly the identification of patients with poor prognosis who are in need for a more aggressive adjuvant approach according to established prognostic parameters and *vice versa.* In this manner, a need to identify patients who will benefit from a particular form of anticancer treatment is obvious. But, we should always ask whether the new factor adds any new information to that already given from the classical prognostic factors.

Despite very intensive investigation in this field, the unique premise concerning the usefulness of "new biomarkers" cannot be elicited. The trouble with the assessment of new prognosticators is that the relevant studies tend to correlate them with each other and with other patients' characteristics. In fact, true validation of a new prognostic marker requires confirmation of its independent prognostic value. Concerning statistical analysis, lack of multivariate analysis is particularly disapproving in the evaluation of the potential prognostic value of a certain marker, especially because p values from univariate analysis depend on the number of the analyzed patients. Since the majority of the investigated biomarkers reflect a small number of relevant biological processes such as cell proliferation and apoptosis, many of these factors may be related to each other or may be representative of the same biological phenomena. Furthermore, the assessment is often done within groups with mixed classical prognostic parameters, impeding a clear output from the investigation. For example, Tan et al. in analysing the prognostic value of p27 in small invasive breast cancer found that this cell cycle inhibitor is an independent prognosticator only in the group of lymph node negative patients [7]. Probably, due to the small number of the included patients, Cianga et al. did not find significantly different incidence of low/high p27 between N- and N+ patients.

Also, in multistage diseases such as cancer, some

marker may be of value in a particular stage of disease, reflecting the particular progression level. Concerning this approach Cianga et al. analyzed p27 expression in primary tumors and their axillary node metastases concluding that p27 phenotype is preserved from the primary tumor to its metastases.

A particular concern in the validation of biomarkers is the lack of standardization of the various methods used for their detection. IHC as a modern and relatively simple method, used by Cianga et al, has certain disadvantages - from the variability in the tissue fixation, use of various available antibodies, each with its own sensitivity and specificity, to the determination of the threshold value and the interpretation of the staining. The question of cut-off values in the assessment of various prognosticators determined by different methods is very important, since for most biomarkers cut-off values are fixed empirically and, hence, they are not always the result of the biological behavior of the tumor.

Using χ^2 test, Cianga et al. did not find any significantly different incidence of low/high p27 levels in relation with the examined classical parameters including menopausal status, tumor size and histological grade as well as in relation with c-erbB-2 and p53 expression. A trend towards higher incidence of p27+ (high level) cases in the prognostically better cases was observed. Since p27 is a cell cycle inhibitor acting in a tumor suppressor manner, its higher expression can be expected in the prognostically better groups. It is possible that statistical analysis of the results from Cianga et al. has been limited by the small number of the patients.

Among the "new generation" markers the selection of c-erbB-2 and p53 by Cianga et al. was probably done because of their role in the regulation of cell proliferation. A growing body of data indicates that abnormalities of both indices are connected with poor prognosis. Although insignificant, lack of p27 expression in tumors overexpressing c-erbB-2 and p53 can be expected.

In the article by Cianga et al. a direct positive correlation between estrogen and progesterone receptors expression and p27 expression was found. Estrogen and progesterone receptors describe estrogen dependence of breast cancer. Progesterone receptor synthesis is stimulated by estrogens and the presence of progesterone receptors is an indicator of an intact estrogen downstream pathway. Since steroid receptors status has prognostic significance concerning disease-free and overall survival in breast cancer patients, it has been assumed that it may be an indirect reflection of tumor aggressiveness. The prognostic significance of steroid receptors status can be dissociated – estrogen receptor status is probably a stronger predictor of disease-free survival, whereas progesterone receptor status better influences overall survival due to its better predictive value concerning endocrine therapy after disease recurrence [8,9]. The advantage of positive steroid receptors status is lost with longer follow-up, indicating that steroid receptors status is a reflection of proliferative capacity rather than metastatic potential. Indeed, estrogen and progesterone receptor levels are inversely correlated in measuring tumor proliferation [8]. Since p27 protein is a cell-cycle inhibitor, the findings of Cianga et al. confirm that steroid receptors status indirectly reflects the proliferative ability of malignant cells.

At the end, it must be mentioned that a considerable body of investigation deals with the multiple and complex mechanisms of cancer development and progression, with an aim to hopefully individualize prognosis and therapeutic disease outcome. Molecular profile of individual tumors is considered to become routine that way, defining thus individual prognosis and optimizing treatment.

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