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ROLE OF PROGNOSTIC FACTORS IN THE MANAGEMENT OF BREAST CANCER

SUMMARY

Prognostic factors should be used to provide an estimate of risk of recurrence in women with early-stage breast cancer. A useful prognostic factor has the following characteristics: it has significant and independent predictive value that has been validated by clinical testing, its determination must be feasible, reproducible, and widely available, with quality control and it must be readily interpretable by the clinician and have therapeutic implications. Tumor diameter, lymph node status and histological grade are the most important prognostic factors in breast cancer. Besides these morphologic parameters numerous biological markers have been determined, but their importance as prognostic factors is still a matter of debate.

The prognostic and therapeutic implications of mammaglobin (MGB1) gene, high intratumoral microvessel density (MVD) and CK19-positive cells positivity in the peripheral blood of breast cancer patients should be the matter of further investigation.

Combination of the single parameters to give complex indexes can yield more information about the biological behavior of each neoplasm. The use of prognostic indexes, especially when compiled using traditional parameters, is a useful aid to the clinician, since they can provide a reliable indication of how individual tumors will evolve.

Key words: breast cancer, prognostic factors, prognostic index

INTRODUCTION

Prognostic factors should be used to provide an estimate of risk of recurrence in women with early-stage breast cancer. Although no individual patient can be assured that she has no risk of recurrence, the majority of women will be cured with local/regional therapy (1).

A useful prognostic factor has the following characteristics:

• It has significant and independent predictive value that has been validated by clinical testing.

• Its determination must be feasible, reproducible, and widely available, with quality control.

• It must be readily interpretable by the clinician and have therapeutic implications.

PROGNOSTIC FACTORS

I Clinical prognostic factors
  for breast cancer

Regional nodal involvement

The extent of regional nodal involvement is the most powerful prognostic factor for predicting probability of recurrence. There is a direct and pro-

portional correlation between the number of axillary nodes involved and probability of relapse. Ten yeass survival ranges from 75% for patients with node-negative tumors to approximately 10–20% for patients with 10 or more involved nodes (2). When present, axillary nodal involvement appears to obscure the prognostic significance of other factors. Immuno-histochemical demonstration of otherwise occult micrometastatic nodal involvement has prognostic significance, but this procedure at the moment is still investigational. Involvement of internal mammary nodes is also prognostically relevant, but this analysis is usually not performed because their involvement is rare in case of negative axillary involvement and mostly limited to inner-quadrant tumors (3).

Tumor size

In cases without axillary involvement, pathologic tumor size is the best predictor of outcome. Five-year recurrence rate ranges from approximately 10% for patients with tumors of less than 1 cm in diameter to approximately 30-50% of patients with tumors of 5 or more cm in diameter (4). However, this might not be the case for slow-growing very large tumors of certain subtypes (i.e. mucinous, papillary, tubular, medullary or adenocystic) that might not have high proliferative capacity. At the moment it is not known if invasive tumors of 1 cm or less in diameter detected by screening mammography might be considered of similar aggressiveness as those detected by physical examination.

II Biologic prognostic factors for breast cancer

Estrogen and progesterone receptor status

Patients with receptor-positive tumors have a better prognosis than those with receptor-negative tumors. However, the difference in recurrence rates at 5 years is only 8 to 10 percent (5).

Nuclear grade

This is a well-documented factor. When determined by experienced pathologists, it discriminates favorable and unfavorable prognostic groups. High nuclear grade is associated with a higher rate of recurrence (6). Nuclear grade is not currently part of the routine pathologic review of breast cancer specimens. The pathology community should adopt a uniform grading system and routinely use this discriminate.

Histologic type

Several well-characterized histologic subtypes impart a favorable prognosis, although they are a distinct minority of all breast cancer cases. These subtypes include tubular, colloid (mucinous), and papillary types (7).

Proliferative rate

Measurements of cellular proliferation in breast cancer specimens using a variety of techniques have shown a strong correlation with outcome. DNA flow cytometry has become widely available for the determination of S-phase fraction as well as ploidy status. S-phase fraction does correlate with prognosis, but ploidy status alone is not of clear prognostic value. Up to 25 percent of specimens are not evaluable by flow cytometry because of methodological problems. Because of the complexity of the technology, quality control is especially critical. Although S-phase fraction has been shown to be an independent prognostic factor in some studies, its clinical value is being defined (8).

Other factors

Other biological factors – such as growth factors regulators or receptors (i.e., c-erbB-1, c-erbB-2, (also called HER2/neu) insulin-like growth factor receptor or somatostatin receptor), tumor suppressor genes (p53 and nm23), cathepsin D, angiogenesis, laminin receptor, heat-shock protein, and tumor growth factor alpha are investigational. The availability of specific drugs, which modulate growth of c-erbB-2 overexpressing cells, and which have already been proven to significantly benefit patients with advanced breast cancer, will allow further trials based on targeting biological pathways in the adjuvant setting. In the future c-erbB-2 determination may be upgraded to become a routine test (1).

New prognostic factors

Dr Sergio Castedo and his team from Portuguese Oncology in Porto (9) developed new one-step RT-PCR assay for the detection of the mammaglobin (MGB1) gene transcript in the peripheral blood of breast cancer patients. Mammaglobin (MGB1) gene is potentional specific marker for circulation tumor cells. This method, using specific primers for cDNA synthesis, proved to be more sensitive than previously reported methodologies.

A positive correlation was seen between MGB1 positivity and breast cancer stage: 0/3 (0%) in stage 0, 3/13 (23%) in stage I, 6/17 (35%) in stage II, 5/10 (50%) in stage III, 8/11 (73%) in stage IV (p = 0.003). The prognostic and therapeutic implications of MGB1 positivity by one-step RT-PCR in the peripheral blood of breast cancer patients, espe-

cially in clinically localized disease (stages I and II), should be evaluated after long-term clinical follow-up of these patients.

In another study, Giatromanolaki et al. (10) from Democritus University of Thrace in Alexandroupolis use two tests for detection intratumoral microvessel density (MVD) and presents of circulation tumor cells in the blood of patients with early breast cancer. Using a nested RT-PCR technique, authors assessed presence of cytokeratin-19 (CK19) mRNA positive cells in the blood of operated patients with breast cancer before the initiation of adjuvant chemotherapy and local radiotherapy, proliferation index and tumor microvessel density (MVD).

Simultaneous display of high intratumoral MVD and CK-19 mRNA-positive cells, characterized highly angiogenic and disseminated disease (HAD). In 25% of patients HAD was noted. Patients with HAD had an expected relapse rate close to 70%.

The simultaneous presence of high MVD and CK19-positive cells in the blood of patients with early breast cancer is linked with poor prognosis, which cannot be improved with standard chemotherapy regimens.

Estimating individual risk

Currently available prognostic factors are associated with a broad range of risk of recurrence in node negative breast cancer patients. There are extremes of high and low risk where it is possible to make recommendations about adjuvant systemic therapy. For example, outside of clinical trials, it is reasonable not to treat patients with tumors less than or equal to 1 cm in diameter because their chance of recurrence is less than 10 percent at 10 years. With increasing tumor diameter, other prognostic factors should be weighed in the decision to use adjuvant treatment. A major goal is the development of risk profile systems with sufficient accuracy and reproducibility to estimate prognosis in the individual patient.

During the breast cancer diagnosis and treatment in Clinical Center Niš we examine almost all clinical and biological prognostic factors. Our routine protocol for breast cancer treatment include preoperative diagnosis of tumor localization, size and consistension. After the breast tumor removal, histopathology examination were performed. Standard examination include the extent of regional nodal involvement, histologic type, nuclear grade and estrogen and progesterone receptor status. Other biological factors - such as growth factors regulators or receptors (i.e., c-erbB-1, c-erbB-2, (also called HER2/neu) insulin-like growth factor receptor or somatostatin receptor), tumor suppressor genes (p53

and nm23), cathepsin D, angiogenesis, laminin receptor, heat-shock protein, and tumor growth factor alpha are not in the routine clinical practice.

Our experiences show that tumor diameter and lymph node status are the most important prognostic factors in breast cancer treatment.

Prognostic index

Measurement of a large number of prognostic factors is of no value in the routine management of patients with breast cancer. Combination of the single parameters to give complex indexes can yield more information about the biological behavior of each neoplasm.

The Nottingham Prognostic Index (NPI), which is used mainly in Great Britain, was used for the first time in 1982 (11). It is based on three traditional prognostic factors: tumor diameter, lymph node status, and histological grade. The NPI was determined from the following formula:

$$NPI = 0.2 \times T\ (cm) + N(1\text{-}3) + G(1\text{-}3)$$

T is the maximum tumor diameter in cm, N the number and level of nodes metastasized (1= no positive axillary lymph nodes; 2 = 1-3 positive axillary lymph nodes or involvement of a node in the internal mammary chain; 3 = more than 3 positive axillary lymph nodes or involvement of both axillary and internal mammary lymph nodes) and G the Elston and Ellis grade. The resulting numerical index gives three prognostic categories:

category 1 = low risk, with NPI equal to
or less than 3.4
category 2 = medium risk, with NPI
between 3.4 and 5.4;
category 3 = high risk, with NPI over 5.4.

The Adelaide Prognostic Index (API) was first proposed in Australia in 1997(3) and was subsequently modified by the adoption of quantitative methods (12). The API was obtained by checking for the presence of one or more of the following unfavorable prognostic factors: (1) tumor diameter greater than 20 mm; (2) positivity for ER in under 30% of neoplastic cells; (3) cell kinetics, using the Ki67/MIB-1 antibody, greater than 10%. When the resulting risk factors are summated it is possible to assign each case to one of the following prognostic categories:

category 0 = low risk, with no risk factors
category 1 = low/medium risk, with only
one risk factor
category 2 = medium/high risk, with two
risk factors
category 3 = high risk, with three risk factors

Prognostic factors for local recurrence after conservative treatment

Close (less than 1 mm), positive or doubtful resection margins, extensive intraductal component (EIC) with involved margins, lymphatic vessel infiltration and young patient age are factors for higher risk of local relapse after conservative treatment (13).

Prognostic factors for loco-regional relapse after mastectomy

The number of positive axillary nodes (3 or more), close or doubtful chest wall or skin resection margins, and tumor size in association with other biological prognostic factors are indicators for higher risk of loco-regional relapse.

Conclusions

Tumor diameter, lymph node status and histological grade are the most important prognostic factors in breast cancer. Besides these morphologic parameters numerous biological markers have been determined, but their importance as prognostic factors is still a matter of debate. Mammaglobin (MGB1) gene is potential specific marker for circulation tumor cells. The prognostic and therapeutic implications of MGB1 positivity in the peripheral blood of breast cancer patients, especially in clinically localized disease should be evaluated. The simultaneous presence of high intratumoral microvessel density and CK19-positive cells in the blood of patients with early breast cancer is linked with poor prognosis, which cannot be improved with standard chemotherapy regimens.

Combination of the single parameters to give complex indexes can yield more information about the biological behavior of each neoplasm. The use of prognostic indexes, especially when compiled using traditional parameters, is a useful aid to the clinician, since they can provide a reliable indication of how individual tumors will evolve.

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ZNAČAJ PROGNOSTIČKIH FAKTORA U LEČENJU KARCINOMA DOJKE

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SAŽETAK

Uloga prognostičkih faktora je u predviđanju stope rizika pojave lokalnog recidiva kod pacijentkinja sa karcinomom dojke. Prognostički faktori moraju da imaju određene karakteristike: da poseduju značajnu i nezavisnu vrednost procene koja se može klinički testirati i dokazati; moraju biti verodostojni, reproduktivni i široko prihvatljivi; moraju biti jasno klinički određeni i klinički primenjivi. Veličina tumora, limfonodalni status i histološki gradus predstavljaju najvažnije prognostičke faktore u lečenju malignih tumora dojke. Pored ovih prognostičkih faktora postoje i brojni drugi biološki markeri koji mogu uticati na prognozu bolesti, mada njihov značaj i danas predstavlja predmet polemike. Terapijska i prognostička uloga mamoglobin (MGB1) gena, intratumorski mikrovaskularni denzitet (MVD) i prisustvo CK19-positivnih ćelija u krvi pacijentkinja sa karcinomom dojke biće predmet daljeg ispitivanja.

Kombinacija pojedinih parametara daje određeni indeks kojim se mogu dobiti adekvatnije informacije o biološkom ponašanju svakog tumora. Upotreba ovih prognostičkih indeksa, naročito ukoliko su sastavljeni od više standardnih prognostičkih parametara, može imati veoma važan klinički značaj, s obzirom da oni mogu dati validne podatke o ishodu bolesti.

Ključne reči: karcinom dojke, prognostički faktori, prognostički indeksi