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TRIPLE NEGATIVE BREAST CANCER – CURRENT STATUS AND PROSPECTIVE TARGETED TREATMENT BASED ON HER1 (EGFR), TOP2A AND C-MYC GENE ASSESSMENT

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Background: Every year about one million women worldwide are diagnosed with breast cancer which is the most common malignancy in female. Of these, triple negative breast carcinoma represents 10–17 %. Triple negative breast carcinomas, characterized by estrogen, progesterone and HER2 receptor negativity are very aggressive tumours with poor prognosis. Individualized treatment (tailored therapy) based on molecular biology markers of tumor and patient is the trend in clinical practice these days. However, molecular targets and predictors for the treatment of triple negative breast carcinoma do not currently exist.

Methods and results: This minireview focuses on biomarkers (HER1/EGFR, TOP2A and C-MYC genes) that may predict the response of triple negative breast carcinoma patients to chemotherapy and/or targeted biological treatment with a summary of current knowledge about them.

Conclusion: HER1 belonging to the HER family of receptors plays an important role in cell proliferation, migration and protection against apoptosis. HER1 protein could be targeted by monoclonal antibodies and/or tyrosine kinase inhibitors (TKIs). Given signal pathway complexity and HER family member cooperation, it may be better to simultaneously target a number of these receptors (e.g. HER1/HER2 by lapatinib). Thus, HER1 assessment could reveal a particular breast cancer patient group with probably good response to HER1 targeted therapy. TOP2A gene, encoding topoisomerase II alpha (target for anthracyclines) is predictive of response to anthracycline therapy. TOP2A aberrations (amplification, deletion) are found in up to approximately 30-90 % of HER2 amplified breast cancer and amplifications are more common than deletions. Recent publications describe TOP2A amplification also in 2.7–8.8 % HER2 nonamplified breast cancers. Patients with a pathologic complete response to anthracycline based neoadjuvant chemotherapy had a good overall prognosis regardless of molecular subtype of breast cancer. These results suggest that particularly tumors with a complete pathological response to anthracyclines could have TOP2A amplification. C-MYC encodes nuclear DNA binding proteins that regulate proliferation and apoptosis; amplification is associated with poor prognosis and hormonally negative breast carcinoma.

INTRODUCTION

About one million women worldwide are diagnosed with breast cancer (BC) every year. BC is the most common cancer in women. Data from the Czech National Oncology Registry (www.svod.cz) indicate the incidence has doubled since 1977 and in 2005 it reached 105.5/100 000 women with a mortality of 36.5/100 000. Due to mamographic screening, stage I of the disease is diagnosed in nearly 35 % of patients and stage II in more than 30 %[1-2]. Triple negative breast carcinoma (TNBC) represents 10-17 % of all BC[3]. This minireview focuses on potential molecular targets and biomarkers that could be aimed or analyzed for prediction of response of TNBC patients to chemotherapy and/or biological targeted therapy.

Pathology and Cytogenetics

Ductal carcinoma is the most common histological category of malignant breast tumors, lobular carcinoma is the second major type while medullary carcinoma is relatively rare entity[4]. On diagnosis, the various presentations are classified on the basis of morphological and molecular examination. Prognosis is defined according to a number of parameters: tumor size and grade, the presence/absence of estrogen (ER) and/or progesterone (PR) receptors, HER2/neu (HER2, c-erbB2) protein, lymph node metastases and vascular or perineural tumor invasion. Other parameters, such as the proliferating index, ploidy, the presence of P53, cytokeratins (Ck), HER1 (EGFR), or TOP2A alterations, may also be useful for prognostic evaluation or as predicting therapeutic re-

sponse. Classification according to immunohistochemistry (IHC) (based on expression profiles) distinguishes HER2+ (HER2+, ER+/–, Ck5/6 and EGFR +/–), luminal (HER2 –, ER+, Ck5/6 and EGFR +/–) and basal-like (ER –, HER2 –, Ck5/6 and/or EGFR +) carcinomas [5-7].

New insights into the molecular pathogenesis of BC, with prognostic and predictive impact, have been gained using cytogenetics. BC tumor genomes have undergone major rearrangements. Hot spots for gains are routinely observed at 1q31-q32, 8q12 and 8q24 (MYC), 17q12 (HER2), 17q23-24 and 20q13, recurrent losses are present at 1p, 6q, 8p, 11q23qter, 13q, 16q, 17p and 22q. The number of changes accumulates in advanced tumors[8-9].

Triple negative breast carcinomas

Triple negative breast carcinomas (TNBC), characterized by absence of ER, PR and HER2 expression, are very aggressive tumors with poor prognosis. They more frequently affect younger patients (<50 years), are more prevalent in African-American women, often present as interval cancers, initially are highly chemosensitive, but are significantly more aggressive than tumors pertaining to other molecular subgroups. This aggressiveness is best illustrated by the fact that the peak risk of recurrence is between the first and third years and the majority of deaths occur in the first 5 years following therapy. The majority of TNBC are high-grade invasive ductal carcinomas of no special type, metaplastic and medullary carcinomas[3, 7].

Individualized treatment (tailored therapy)

Personal, custom made, therapy based on molecular biology markers of tumor and patient is the trend in clinical practice these days. The first clinically used predictive markers in BC were ER/PR tailoring response to antihormonal therapy[10-11]. The first cytogenetic predictor for BC treatment is the HER2 (HER2/neu, c-erbB2) gene amplification and protein overexpression. Monoclonal antibody trastuzumab (Herceptin) is used in the treatment of BC in patients who display HER2 positivity in invasive carcinoma component[12-16]. Nevertheless, predictors for the therapy of TNBC do not exist yet.

HER1 gene and targeted therapy

HER1 (also known as epidermal growth factor receptor, EGFR) belongs to the HER family of transmembrane receptors. HER1 gene is located on 7q12. Its protein product – 170-kD glycoprotein – plays an important role in cell proliferation, migration and protection against apoptosis mediated by subsequent activation of intracellular pathways. HER1 receptor can dimerize with all members of HER family and it has to create homo – or heterodimers to be functionally active[17]. Worse prognosis of breast tumors overexpressing HER1 is connected with the above-mentioned effects on proliferation, migration and apoptosis. A study by Filardo et al. focuses on a receptor called G protein-coupled receptor 30 (GPR30), a member of the seven transmembrane receptor superfamily which is associated with specific estrogen binding and HER1 activation[18]. This crosstalk between receptors together with the described influence on cell biology makes HER1 status assessment valuable even in the context of tumor hormonal dependence.

HER1 protein could be targeted by monoclonal antibodies and/or synthetic tyrosine kinase inhibitors (TKIs). Monoclonal antibodies (cetuximab, panitumumab) are now clinically used in the treatment of colorectal cancer and head and neck carcinoma. TKIs are also important in the therapy of pancreatic and non-small cell lung cancer (NSCLC). HER1 targeted treatment with cetuximab in breast cancer have not produced satisfactory results probably because of the activation of downstream signal pathways[7] or inadequate patient selection. TKIs are an option for targeted therapy in BC that is focused on HER1 in particular. Agrawal et al. evaluated the results of studies testing TKIs (erlotinib, gefitinib) in BC and pointed out that HER1 protein must be present in targeted tumor tissue to obtain valuable treatment results. They also concluded that because of signal pathway complexity and HER family member cooperation it might be better to target more of these receptors at the same time[19]. Thus, HER1 assessment could reveal a particular BC patient group with probably good response to HER1 targeted therapy. Dual HER1/HER2 inhibitor lapatinib is now approved for BC patients with HER2 amplification/overexpression when trastuzumab therapy has failed. However, HER1 gene status is not used in clinical practice to guide therapy in BC, although increased HER1 expression is detected in about 40 % of BC. Particularly, HER1 expression is higher (up to 80 %) in TNBC and metaplastic carcinoma (mostly basal-like), where it possibly substitutes ineffective, but otherwise major proliferation/survival pathways of BC induced by expression and activation of HER2, ER and PR proteins. HER1 gene is amplified in nonselected series in 0-14 %, in metaplastic carcinoma up to 28 %[20-26]. Interestingly, HER1 and C-MYC coamplification can be also present[24]. More insights into significance of HER1/HER2 status in outcome of patients treated with TKIs should provide undergoing phase II clinical trial which examines the effect of lapatinib monotherapy in metastatic breast cancer patients with HER2 positive vs. HER1 positive circulating cells in peripheral blood[27].

TOP2A

The TOP2A gene, located on 17q21-22, encoding topoisomerase II alpha (molecular target for anthracyclines) is predictive of response to anthracycline therapy. TOP2A aberrations (amplification, deletion) are found in up to approximately 30-90 % of HER2 amplified BC and amplifications are more common than deletions. Good response to anthracyclines is associated with TOP2A amplification while deletion may be accompanied by resistance. On the other hand, clinical study results are not uniform. Knoop et al. reported in a nonselected series, an association between TOP2A amplification and good response to anthracycline based regimens. Surprisingly, better response to anthracyclines than CMF [cyclophosphamid, methotrexat, 5-fluorouracil (5-FU)] was found in subgroup of patients with TOP2A deletion compared to normal TOP2A status[12, 28-36], probably demonstrating high-

er overall efficacy of antracycline based therapies. One recent study showed that TOP2A deletion was associated with poor prognosis in HER2 amplified BC. Clarification of the mechanism of this association will require additional studies[37]. Burgess et al. identified in a nonselected series, TOP2A expression levels as major determinants of response to the topoisomerase II inhibitor doxorubicin and showed that suppression of TOP2A levels produces resistance to doxorubicin in vitro and in vivo[38]. However in the case of TOP2A there is no correlation between amplification and overexpression[28, 39]. Moreover, our study in locally advanced BC showed HER2 and TOP2A gene status changes after antracycline based chemotherapy[40], and thus number of published data can be biased by treatments preceding tumor biopsy.

Recent publications describe TOP2A amplification in 2.7–8.8 % of HER2 non-amplified BC[35, 41-43]. Tan et al. found TNBC associated with TOP2A protein expression and poor response to adjuvant anthracyclines; in this study including 31 cases of TNBC TOP2A amplification was not detected using chromogenic in situ hybridization[25]. However, as pointed out above, in contrast to HER-2 status, there is no correlation between TOP2A gene amplification and overexpression[28, 39]. Patients with basal-like BC (overlapped with TNBC)[3] treated with neoadjuvant anthracyclines also have poor prognosis (distant disease free survival, DDFS and overall survival, OS)[44]. It may be hypothesized that the lack of HER2 and TOP2A co-amplification could be the cause. However, patients with a pathologic complete response to anthracycline based neoadjuvant chemotherapy had a good prognosis regardless of subtype (basal-like, luminal-like, HER2+/ER-) (TN paradox)[44]. These results suggest that at least individuals with a complete pathological response to anthracyclines could have TOP2A amplification or overexpression. Unfortunately, in the above discussed study by Carey et al. TOP2A status was not assessed. Weigelt et al. studied metaplastic BC (a subgroup of TNBC) by microarray expression analysis and found significant downregulation in PTEN and TOP2A which might partly explain observed differences in response to chemotherapy in TNBC[45].

C-MYC

The 8q chromosome arm that harbors the C-MYC gene is frequently altered in BC. C-MYC encodes nuclear DNA binding proteins that regulate proliferation and apoptosis. The MYC protein is directly involved in regulating more than 1500 genes[46-52]. C-MYC amplification is one of the most frequent aberrations in BC that has been detected in 1-94 % of patients in different studies. Amplification is clearly associated with poor prognosis: patients suffer from early relapses and have poor OS. C-MYC amplification is associated with ER – and PR – breast carcinoma. C-MYC deregulation occurs preferentially in young patients[53]. C-MYC protein may affect the response to chemotherapy probably through DNA damage response regulation[46, 54-60]. Interestingly, C-MYC amplification in colon carcinoma predicts better response to 5-FU adjuvant chemotherapy [disease free survival (DFS) and OS have been improved by 30 %], but only in p53 wild tumors[61-62]. This type of study in BC has not been published. Nonetheless, Rakha et al. described improvement of the poor prognosis of TNBC by treatment with the CMF regimen[63]. TNBC often have amplified HER1 gene[21] and according to the described C-MYC coamplification in BC[24], so we may hypothesize the possibility that the tumors responding favorably to the 5-FU containing regiment CMF were those with C-MYC amplification. Suppression of C-MYC transcription in BC cells after 5-FU treatment supports the direct effect of 5-FU on the oncogene activity, probably mediated by upstream signaling inhibition[64].

Adjuvant/neoadjuvant chemotherapy

Adjuvant chemotherapy is recommended according to the international guidelines for patients in clinical stage IB to IIIB of breast carcinoma, when the tumor is larger than 1cm and/or lymphonodes are positive, respectively. However in TNBC even smaller tumors are recommended to consider adjuvant chemotherapy with respect to diseases recurrence risk and high aggressivity of this tumor type. For treating TNBC, anthracycline regimens are mostly used[65]. However, there are no data on the real patient benefits. It is assumed that chemotherapy is more successful in ER – than ER+ patients and appears to be more appropriate for young premenopausal women[10-11, 66]. Since the chemotherapy has serious side-effects, finding an accurate predictor of response could determinate patients who would profit from adjuvant chemotherapy. However, current knowledge indicates the possibility of CMF renascence in treatment of TNBC associated with poor prognosis and limited therapeutic options, particularly in adjuvant settings. It is hoped that poor prognosis of TNBC could be improved using CMF treatment[25, 63].

Neoadjuvant chemotherapy is a newer possibility recommended for patients with expected good response to chemotherapy administration (ER-, PR-, non-lobular, fast proliferating, luminal B and high grade tumors), mainly in patients with locally advanced disease potentially indicated for breast saving surgery. Currently applied regimens are mostly based on a combination of anthracyclines and taxanes which suggests again the importance of further comparative studies evaluating the efficacy of CMF, anthracycline based or other therapies in TNBC[65].

CONCLUSION

Triple negative breast carcinoma (TNBC) represents 10-17 % of all BC[3] with poor prognosis. Specific predictors for its targeted treatment are still lacking. However, TOP2A status could predict sensitivity to anhracycline therapy in a small proportion of TNBC patients. Chemotherapy optimization (CMF vs. other regimens) needs to be evaluated in large clinical studies. The complexity of intracellular signal transducing pathways also demands further investigations. This raises the importance of dual inhibitors like lapatinib or molecules preventing dimerisation of receptors like pertuzumab at the

level of HER2 and other members of the HER family[19]. Together with the treatment approaches described there is also the possibility of combination with drugs acting at lower levels of signal transmission.

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