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LETTERS TO THE EDITOR

Different subtypes of metaplastic breast cancer might have different sensitivity to neoadjuvant chemotherapy

Dear Editor,

Metaplastic breast carcinoma (MetaBC) is a rare tumor of breast cancer, often associated with a poor prognosis. MetaBC is frequently regarded as triple-negative phenotype. Histologic variants in the metaplastic carcinoma include matrix-producing carcinoma, spindle cell carcinoma, squamous cell carcinoma, mixed types of MetaBC, low-grade adenosquamous carcinoma, and fibromatosis-like MetaBC. Neoadjuvant chemotherapy (NAC) has been increasingly used as part of the multidisciplinary management of MetaBC [1]. Al-Hilli and his colleagues [2] investigated the clinical and pathological complete response rates (pCR) of MetaBC to NAC. They found that MetaBC is poorly responsive to NAC, with a pCR rate of 11%. The authors did not mention which subgroup of MetaBCs got the most benefit from NAC. Han et al. [1] analyzed 29 patients with MetaBC received NAC. Five (17%) patients achieved pCR. None of the 11 MetaBC with squamous differentiation in the current study achieved pCR after NAC. Interestingly, matrix-producing morphology was associated with higher probability of achieving pCR (p=0.027) [1]. Matrix-producing type MetaBC was one of the most common types of MetaBC in both studies [1,2]. This finding supports that different subtypes of MetaBC might have different sensitivity to NAC and should be further confirmed in larger multi-institutional studies.

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EGFR amplification and mutations landscape in laryngeal squamous cell carcinoma

Dear Editor,

Targeted therapeutic strategies based on monoclonal antibodies (mAbs) and tyrosine kinase inhibitors (TKIs) are applicable in sub-sets of patients with solid malignancies in modern oncology. Concerning these patients, genetic signature and not gross pathological type of the malignancy is the basis for the optimal specific molecular management. Growth factor receptors are proteins that critically affect prognosis correlating with advanced disease in epithelial malignancies. Epidermal Growth Factor Receptor (EGFR-gene locus:7p12, exons:30) encodes the corresponding protein that acts as a transmembrane glycoprotein. It consists of a large extracellular ligand-binding region, a single hydrophobic transmembrane bridge adjusting to an intracellular juxtamembrane (JM) region, a tyrosine kinase domain and finally a C terminal tail with multiple tyrosine residues acting as a regulatory region. Three main EGFR depended pathways have been already identified including the PI3K-AKT-PTEN-mTOR, the RAS-(B) RAF-MEK-ERK/MAPK and also the IL6-JAK1/2-STAT3 [1]. In non-small cell lung carcinoma (NSCLC), EGFR mutations (missense substitutions, inframe insertions, inframe deletions) and amplification modify the response rates (affordable response or activated resistance) to TKIs, such as erlotinib, gefitinib, afatinib, dacomitinib, vandetanib and anti-EGFR mAbs, such as cetuximab, respectively, affecting also the survival status of the corresponding patients [2]. Interestingly, EGFR gene amplification as a strong mechanism leads to protein overexpression in membranous and also diffuse cytoplasmic pattern especially in some transglottic carcinomas [3].

Although EGFR overexpression is frequently observed (30-85%) in laryngeal squamous cell carcinoma (LSCC), amplification and mutations are detected in about 50% of these cases. The majority of applied molecular techniques involved in EGFR gene analyses are based on one-step real-time polymerase chain reaction (PCR) and fluorescence *in situ* hybridization (FISH). Mutation potential is varied in LSCC cases and molecular studies have shown different patterns and percentages (0-16%). The majority of applied molecular techniques involved in these studies are based on one-step real-time PCR. Exons 19 and 20 represent the main intra-gene nucleotide targets for point missense mutations, whereas two silent mutations (T785T and R836R) have been also detected [4,5]. In fact, a low incidence of EGFR mutations in LSCC has been confirmed. Additionally, the study groups identified specimens with gene amplification in the corresponding examined groups of patients. Understand-

ing the gene deregulation mechanism in LSCC EGFR overexpressed cases is a crucial approach. On the other hand, EGFR intra-tumoral heterogeneity in protein expression and different expression patterns due to phosphorylation of the molecule combined with borderline or limited immunohistochemical analysis are biological and technical factors that negatively modify the optimal evaluation of protein expression. For these reasons, genetic analyses provide more accurate data to oncologists in order to handle LSSC patients with mAbs or TKIs.

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Hormone receptor status might be a determinant for HER2 loss after HER2-targeted treatment in HER2 positive breast cancer patients

Dear Editor,

Current literature did not reveal that HER2-targeted treatment more commonly leads to HER2 loss in hormone receptor-negative and HER2-positive tumors than luminal B and HER2-positive tumors. Ignatov and colleagues [1] investigated HER2 discordance and relation to HER2-targeted treatment in 227 patients with primary breast cancer. They reported that the interval between anti-HER2 treatment and the determination of HER2 in second histology was strongly associated with HER2 expression. The authors did not give information about the hormone receptor status of all these 227 HER2 positive patients. My assumption is that HER2 loss might be more frequently seen in hormone receptor-negative and HER2-positive tumors. Interplay between estrogen receptor and HER2 signalling pathways might prevent HER2 loss after HER2-targeted treatment. This issue merits further investigation.

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Chronic antibiotic use for severe acne might increase breast cancer risk

Dear Editor,

Acne vulgaris, one of the most prevalent skin conditions affects more than 85% of teenagers. Although most acne cases recover spontaneously, about 40% of individuals (severe acne) require clinical treatment for acne during early adulthood. Severe acne is usually treated with isotretinoin or systemic antibiotics [1]. Murphy and colleagues [2] investigated whether severe acne was associated with incident breast cancer. In this large prospective study, they observed a statistically non-significant positive association between breast cancer and diagnosis of severe acne, particularly among women who experienced severe acne during adolescence. The authors explained the association between severe acne and increased breast cancer risk by elevated sex hormones early in life. Interestingly, women who reported ever using systemic antibiotics for acne treatment were more likely to develop breast cancer than women who did not. The authors did not mention any possible association between chronic antibiotic use and increased breast cancer risk. Two large studies showed that antibiotic use, specifically with chronic use, has been associated with increased risk of breast cancer [3,4]. Use of antibiotics may be associated with risk of breast cancer through effects on immune

function, inflammation and metabolism of sex hormones. This issue merits further investigation.

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K-RAS mutations in laryngeal squamous cell carcinoma

Dear Editor,

In solid malignancies, a variety of gene functional and numerical imbalances affecting crucial molecular pathways such as cell cycle regulation, signaling transduction, apoptosis or angiogenesis have been identified and explained. Cell malignant transformation is mediated by an aberrant gene expression, including predominantly oncogenes up regulation combined with suppressor genes down regulation that lead to cell cycle deregulation. In fact, cancer genome consists of all genetic alterations that modify the normal DNA/m RNA sequences triggering a cataract of molecular reactions inside and outside the nucleus micro-environment. Point mutations, polymorphisms, abnormal gene copy number (amplification, deletion), or structural chromosomal rearrangements (translocations) and epigenetic modifications detectable by different molecular techniques provide critical information to oncologists for handling those patients in a rational therapeutic way regarding their isolated molecular landscape. Growth factor receptors (GFRs)-depended signaling pathways include mainly the PI3K-AKT-PTEN-mTOR, the RAS-(B) RAF-MEK-ERK/MAPK and also the IL6-JAK1/2-STAT3 [1].

Among oncogenes, the Kirsten ras oncogene homolog (KRAS, Cytogenetic Location: 12p12.1) represents an important family of genes (proto-oncogenes) –including also HRAS and NRAS – that encode proteins acting as hydrolase enzymes, especially hydrolyzing guanosine triphosphate (GTPases) [2]. They promote cell division, cell differentiation, and also indirectly programmed cell death (apoptosis). Deregulation of KRAS is detected frequently in solid malignancies as a result of point mutations. Concerning Laryngeal Squamous Cell Carcinoma (LSCC), mutation potential of the oncogene seems to be low focused mainly on codon 12. A study group co-analyzing Epidermal Growth Factor Receptor (EGFR) and KRAS genes implemented high resolution melting analysis (HRMA) and one-step real-time polymerase chain reaction (PCR), especially for EGFRvIII. They concluded that a very limited rate of KRAS mutations characterizes the examined Belgian population with Head and Neck Squamous Cell Carcinoma (HNSCC) including LSCC cases (7.0% of the specimens, only one case with point mutation) [3]. Similarly, another study group identified only two cases were KRAS mutant at codon 12, whereas EGFR exons 19 and 20 point missense and deletion mutations were detected in significant proportions combined or not with gene amplification [4]. Additionally, absence of KRAS mutations in codons 12 and 13 of LSCCs, whereas EGFR overexpression was prominent in the corresponding Japanese patients analyzed for the markers by another study [5]. Based on these studies, it seems that KRAS demonstrates low mutational rates in HNSCC, and especially in LSCC cases. KRAS wild-type combined with EGFR deregulation (point mutations and/or amplification) is a frequent genetic signature in these patients. Although mutant KRAS remains a challenging therapeutic target in a variety of solid malignancies, its clinical significance and impact in LSCC is under consideration.

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Deciphering trastuzumab resistance in residual tumor according to HER2 status after neoadjuvant trastuzumab containing regimen in HER2 positive breast cancer patients might help to choose further adjuvant anti-HER2 treatment

Dear Editor,

Patients who have residual invasive breast cancer after receiving neoadjuvant chemotherapy (NAC) plus trastuzumab have a worse prognosis than those who have no residual cancer. The current standard of adjuvant systemic treatment in patients with HER2 positive disease is completion of 1 year of HER2-targeted therapy, most commonly trastuzumab [1]. Recently, KATHERINE trial that showed that in HER2 positive patients who received NAC including HER2 targeted agents and had residual disease had improved survival if received one year of trastuzumab-emtansine (T-DM1) rather than just trastuzumab (+endocrine therapy if ER+), supporting T-DM1 as new adjuvant standard in high-risk HER2 positive breast cancer [2]. However, HER2 status in residual tumor was not defined in this study. We propose that persistence of HER2 positivity in residual tumor might show real trastuzumab resistance that should not be treated with trastuzumab and T-DM1 works better in this residual subgroup. In contrast, HER-2 loss in residual tumor might reveal that these tumors are sensitive to trastuzumab and should be further treated with adjuvant trastuzumab. This issue merits further investigation.

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