Targeted Therapy in Breast Cancer

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Due to an increased knowledge on how to run well-designed clinical trials, development of cancer drugs has evolved substantially, including cytotoxic agents, endocrine agents and new-generation targeted drugs. However, the major aims are still to register and establish new drugs for broad groups of rather unselected patients based on crude conventional classification systems. As in general only a small group of patients experiences an advantage, current trials must have large sample sizes to be able to detect small efficacy differences. Despite this, significant achievements have been made for breast cancer with the use of new drugs in the metastatic and the adjuvant setting [1, 2]. These improvements, however, have been paid for by overtreatment and undertreatment of large cohorts of patients.

In parallel, there have been remarkable improvements in molecular and functional understanding of normal breast tissue development and breast cancer. Breast cancer is no longer one disease entity. Retrospective RNA expression profiling and reverse transcriptase polymerase chain reaction (RT-PCR) based studies have defined distinct subgroups with different prognoses requiring different clinical management [3–8]. Therefore, it is time to finally leave the ‘one fits all’ strategy. Two signatures, which are currently tested in the Microarray in Node-Negative Disease May Avoid Chemotherapy Trial (MINDACT) and the Trial Assigning Individualized Options for Treatment (TAILORx) trial, will hopefully help to reduce adjuvant cytotoxic overtreatment in the near future. Given the huge amount of new targeted drugs currently in preclinical and clinical development as outlined by the comprehensive overview of Joachim Bischoff and Atanas Ignatov in this issue of BREAST CARE [9], it is time to prospectively integrate more molecular and biologic knowledge into oncological study designs. New targeted drugs will potentially only be effective in small subgroups of breast cancer patients based on prospectively proven marker signatures or functional characteristics rather than on morphology or single markers alone.

Currently targeted drug selection in breast cancer is exclusively based on estrogen receptor (ER), progesterone receptor (PgR) and human epidermal growth factor receptor (HER2) expression mainly of the primary tumor, even if metastatic disease is actually treated. Retrospective data indicate discordance regarding those factors between primary tumors and corresponding metastatic lesions in up to 44% of patients, which would even require alterations during palliative treatment [10–13]. For better patient selection this indicates the need for prospective target evaluation not only in the primary tumor but also in metastatic lesions.

In addition, for treatment evaluation it is essential to obtain data on whether the targeted drug administered actually reaches the target and results in inhibition of function. This strategy requires repeated biopsies. A biopsy of one lesion, however, may miss important target heterogeneity in particular in the metastatic setting. Therefore, target-specific functional imaging techniques need to be developed in parallel. As it is feasible to perform sequential tumor biopsies and evaluate functional imaging techniques, the neoadjuvant setting is an excellent research strategy to obtain those data. Furthermore, in patients other and more complex mechanisms may be important than in test tubes. Therefore, we should concentrate our efforts regarding biomarker development on the in vivo situation and no longer promote in vitro chemosensitivity and resistance testing.

We all know that if trastuzumab combined with chemotherapy had been developed without preselection of patients with HER2-overexpressing breast cancer, we would probably never have demonstrated any improvement in survival [14]. Consequently, one of the most successful drugs in HER2-overexpressing breast cancer never would have been approved. Only by preselecting patients with HER2-overexpression, it has been possible to detect significant and substantial survival benefits of several months even in small studies of only 469 and 192 patients, respectively [15, 16]. In this issue of BREAST CARE Michael Untch nicely reviews our current knowl-

edge regarding treatment of early and locally advanced breast cancer with molecular targeted therapies that are already approved or in advanced clinical development [17].

Preliminary clinical data with sorafenib, a tyrosine kinase inhibitor (TKI) mainly targeting vascular endothelial growth factor receptor-1–3, platelet-derived growth factor- α and - β , RET, Flt3 and c-KIT, indicates that it seems to have only minor efficacy in an unselected group of metastatic breast cancer patients with no response detected according to conventional end point definitions [18]. Is this the end of the story of sorafenib in breast cancer or have we simply not treated the right patients so far? We do not know. In order to select the correct targeted drug from the long list of drugs for the right patient at the right time in the right dose, drug selection

and dosage has to be based on a detailed and comprehensive molecular characterization of the tumor and, of course, the host on the genome, epigenome, transcriptome and protein level in the future.

This is a long way to go, but we are forced to do so, because the present European Medicines Agency (EMA) guidelines for anticancer medicinal products urge investigators of non-cytotoxic compounds to analyze biopsies of primary tumors, normal tissues, and metastatic lesions to understand the target and downstream effects and to make use of sensitive imaging techniques [19]. The potential value of targeted drugs can only be revealed by improved patient and target selection. We should really aim at true tailored concepts when exploring new drugs and when investigating their most optimal use.

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