Adjuvant Therapy in Breast Cancer – Have We Already Learned the Entire Lesson?

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At first glance, adjuvant therapy of early breast cancer appears to be a dull topic: the major players are set and have not changed significantly over the last years: chemotherapy, endocrine therapy and HER2 targeted therapy. While during the 1990ies and 2000s a wealth of new substances, such as taxanes, aromatase inhibitors, new-generation bisphosphonates, and HER2 targeted agents, were introduced into the treatment of primary breast cancer, little has been added to this portfolio of substances since then. Indeed, in Europe no new drug has been approved by the EMA for the treatment of early breast cancer during this decade.

So, nothing new to be learned and discussed?

Paradoxically, within the last 6 months, both the San Antonio Breast Cancer Symposium (SABCS) 2013 and the Annual Meeting of the American Society of Clinical Oncology (ASCO) 2014 focused on early breast cancer and provided progress on answering a number of open questions, which could not be resolved yet:

- Which patients do need chemotherapy in the context of hormone responsive disease? The emerging evidence on gene expression tests, the implementation of molecular and immunohistochemical subtypes and the reduced risk for relapse overall generated the diversification of decision-making beyond the traditional St. Gallen Risk Criteria. Current national and international guidelines struggle with setting a standard within an ongoing debate.
- Tumor risk versus tumor biology: to what extend do we still need conventional risk factors, such as axillary lymph node status? Based on the ACOSOG Z0011 trial and other evidence, systematic axillary dissection is performed in fewer and fewer patients. Does this influence our decision-making on indication and type of (neo)adjuvant therapy, or should we rely more heavily on tumor biology?
- Clinical and translational research in the neo-adjuvant setting in Germany has set worldwide standards. Primary systemic treatment has become a standard option for all patients with need for chemotherapy. However, the optimal timing of systemic and surgical treatment is still not defined in many patients and the prognostic relevance of pathological complete response may differ from subtype to subtype. Innovative neo-adjuvant treatment strategies with

novel agents or as endocrine treatment responsiveness testing (such as in the WSG Adapt study) will optimize treatment, while daily clinical practice still needs to be defined in many settings.

- One of the big ASCO surprises in 2014 was the negative ALTTO study, which showed no superiority of the dual targeted treatment arm compared to trastuzumab. Given the fact that the combination of trastuzumab and pertuzumab has already been approved by the Food and Drug Administration (FDA) in the US, but not by the corresponding authorities in Europe, these results will trigger a discussion on the use of dual targeted anti-HER2 treatment in early breast cancer. While dual targeted treatment has been established in the treatment of advanced breast cancer, its role is still unclear in early breast cancer.
- The negative ALTTO trial at ASCO 2014 also renewed the discussion on the translation of neoadjuvant response data, especially the results on pathological complete response (pCR) into actual survival benefits. While the FDA meta-analysis provided evidence both for HER2-positive and triple-negative early breast cancer, the pCR benefit from Neo-ALTTO did not translate into a survival benefit within the ALTTO-study. The validity of pCR results and the question which patients benefit most from neoadjuvant treatment will be discussed in this issue. In my view there is no doubt that a considerable number of our patients currently benefit and will benefit in future from neoadjuvant treatment.
- While the stage of endocrine treatment appeared to be set without immanent alterations, arising data on extended adjuvant endocrine treatment over 10 years and the new data on the combination of aromatase inhibitors and ovarian function suppression also revived the discussion on optimal endocrine treatment, both in the pre- and postmenopause.

There is no lack of topics to be discussed and put into new perspective concerning the adjuvant treatment of early breast cancer. This issue of BREAST CARE will give you an overview of the current state of the art.

Enjoy both the reassurance of those aspects that we know are of benefit to our patients, but also the controversy of the aspects which we need to address within the coming years.