TREATMENT OF EARLY HER2+ BREAST CANCER: ACHIEVEMENTS AND UNMET NEEDS

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CONTE PierFranco, PIACENTINI Federico
Dept. of Oncology, Hematology and Respiratory Diseases – Modena University Hospital

Among breast cancers diagnosed at any stage, 20%–30% are found to have HER2 gene amplification/receptor overexpression that is associated with aggressive behaviour (high proliferative activity, metastatic potential and neoangiogenesis) and poor outcome. Trastuzumab, the humanized monoclonal antibody against HER2 receptor, is an essential component of the treatment of patients with HER2-positive breast cancer that has change the biological history of the disease.

In the adjuvant setting, the results of six phase III randomized trials with more than 10,000 HER2-positive breast cancer patients have been presented so far; different chemotherapy regimens and different modalities of trastuzumab administration (in combination or sequentially after chemotherapy) have been explored. Five trials have demonstrated the superiority of adding trastuzumab to chemotherapy compared with chemotherapy alone (the DFS was 33%–52% greater independently from age, nodal status, hormonal status, or tumor size and the OS was 34%–41% greater), while only PACS04 trial has shown no benefit for adding trastuzumab at the completion of chemotherapy versus control. The majority of these trials have tested one year of trastuzumab therapy. But the HERA trial is the only one specifically designed to test prospectively different durations of trastuzumab administered with sequential approach (that is at the end of adjuvant chemotherapy), with positive results in terms of DFS and OS; up to now, the results of the comparison of 1 versus 2 years of treatment are still not yet available. Moreover, the cytotoxic synergism of combined trastuzumab and chemotherapy is supported not only by the previous mentioned trials, but also by clinical data in metastatic (25% survival increase) and neoadjuvant settings (26.3% of pCR without and 66.7% of pCR with trastuzumab respectively in the MDACC experience). Interestingly, a small Finnish study wherein trastuzumab was administered for a very short period (9 weekly administrations) concomitantly with chemotherapy suggested that a shorter treatment might produce comparable efficacy with significant lower toxicities. The cardiac safety of trastuzumab is in fact another relevant clinical issue, particularly when it is used as adjuvant therapy. In all the adjuvant trastuzumab trials, despite the selection of the optimal patient population, symptomatic congestive heart failure occurred in 1.5%-2.5% of the patients treated with sequential trastuzumab (HERA trial, PACS 04, and N9831 arm B) and in a percentage ranging from 0.4 (BCIRG006 arm C, without anthracyclines) to 3.6 of the patients in the trials in which trastuzumab was started concomitantly with chemotherapy (BCIRG 006 arm B, N9831 arm C, NSABP B-31); moreover, a significant proportion of patients never started trastuzumab because of LVEF decline (1.9-6.4%) or did not complete the planned trastuzumab therapy due to cardiac events (6-18%). To test the hypothesis that a shorter duration of adjuvant trastuzumab concomitant with chemotherapy might be effective but less toxic, we have designed a phase III multicentre, randomized trial in order to evaluate if short (9 weekly

administrations) versus long (18 three-weekly administrations) adjuvant trastuzumab combined with chemotherapy is equally effective in terms of DFS, and less toxic from a cardiac viewpoint. Other European trials are addressing the same questions (PHARE trial, SOLD trial, PERSEPHONE trial), but in addition this trial will explore less intensive adjuvant trastuzumab regimens in the node negative pT1a,b HER2 positive breast cancer population so poorly represented in most clinical trials.

At the same time, Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation (ALTTO) is a four-arm randomized trial designed to compare adjuvant trastuzumab and lapatinib in women with early-stage HER2-positive breast cancer: it examine which anti-HER2 agent is more effective and which is the best schedule of administration, namely, what benefit will be derived by taking the drugs separately, in tandem order or in combination. Moreover, the TEACH trial is designed to determine whether adjuvant therapy with lapatinib for 1 year will improve DFS. Finally, the strategy for using adjuvant trastuzumab monotherapy with or without endocrine therapy, for tumors judged to be low risk by routine clinico-pathological or molecular assessment is till controversial.

In summary, many questions related to trastuzumab use in the adjuvant setting still remain unanswered, regarding to the optimum timing and duration of treatment, its role in small node-negative tumors, the optimum therapy regimens.

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