Neoadjuvant treatment of HER2-positive breast cancer: should therapy differ based on hormone receptor status?

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Since the advent of trastuzumab, HER2-positive early breast cancer (EBC) has ceased to be an insurmountable threat. In this issue of Therapeutic Advances in Medical Oncology, Basho and McArthur summarize the current evidence regarding targeted therapy in HER2+ EBC.[1]

It has been found that 1 year of adjuvant trastuzumab together with (neo)adjuvant chemotherapy substantially improves, not only disease-free survival, but also overall survival and thereby the chances of a cure for patients with HER2+ disease. Over the last few years, neoadjuvant therapy has become a standard of care in HER2+ EBC[2] and this standard has recently been confirmed by the St. Gallen Consensus for stage II and III HER2+ disease.[3]

The NOAH trial showed for the first time that pathological complete response (pCR) rates are almost doubled by adding anti-HER2 targeted therapy already in the neoadjuvant setting in HER2+ disease.[4] The AGO TECHNO trial showed for the first time that patients who achieve pCR after anti-HER2 therapy plus chemotherapy have substantially better outcomes than patients with non-pCR.[5] The favorable impact of pCR on outcomes in HER2+ disease was subsequently confirmed in a United States Food and Drug Administration (US FDA) meta-analysis comprising almost 12,000 patients with EBC.[6] Meanwhile, dual HER2 blockade with trastuzumab and pertuzumab together with chemotherapy has been registered for HER2+ high-risk EBC. This registration was based on the small phase II NeoSPHERE trial[7] together with the totality of the evidence (i.e. the overall survival advantage in the CLEOPATRA trial)[8] and the fully recruited and subsequently published adjuvant trial APHINITY.[9]

In recent years, evidence has accumulated that not only the course of disease but also response to chemotherapy plus targeted therapy in HER2+ EBC differ according to hormone receptor (HR) status. In the randomized trastuzumab trials in EBC, the proportional benefit from trastuzumab is clearly similar in the HR+ and HR− subgroups. Nevertheless, the relapse patterns differ over time with earlier relapses being observed in the HR− subgroup.[10] In the neoadjuvant setting, the US FDA meta-analysis demonstrated that pCR rates and their impact on outcomes in HER2+ disease substantially depend on HR status with higher pCR rates and a particularly strong prognostic impact in HER2+ HR− disease.[11]

So far, despite these outcome differences according to HR status, current national and international guidelines do not take endocrine sensitivity into account for their recommendations on optimal therapy in HER2+ EBC. In the HR+ subgroup, adjuvant endocrine therapy is considered standard. Yet, the recommendations regarding targeted agents and chemotherapy in the (neo) adjuvant setting do not take HR status into account.

So far, aside from the establishment of dual antibody-based HER2 blockade as a standard, current approaches to improve neoadjuvant therapy in HER2+ EBC have mainly focused on improving the chemotherapy component. There seems to be similar efficacy for anthracycline-based

taxane-containing regimens or a taxane-platinum combination. Independent of the chemotherapy regimen, pCR rates in the HR+ subgroup are consistently lower than those in HR− tumors. Nevertheless, patients with HR+ HER2+ disease generally have a rather good prognosis even in cases with non-pCR. Consequently, patients with HR+ HER2+ EBC may be over-treated by current chemotherapy-based neoadjuvant therapy.

As there is substantial cross-talk between growth factor- and hormone-receptors, it is not unreasonable to assume that one may be able to reduce the chemotherapy component in the HR+ subgroup without compromising efficacy by optimizing targeted therapies. The ADAPT HER2+/HR+ sub-trial showed that combining endocrine therapy with trastuzumab does not render clinically acceptable pCR rates, at least not after 12 weeks of therapy. Interestingly, T-DM1 led to pCR rates quite comparable to more extensive chemotherapy plus targeted therapy, and its efficacy was not altered by adding endocrine therapy.[11] Dual targeted therapy (lapatinib and trastuzumab) together with endocrine therapy again for only 12 weeks showed promising pCR rates even in rather large tumors but also a substantial number of near-pCRs (pT1a-b) in the HR+ subgroup.[12] As Rimawi and colleagues observed fewer near-pCRs in the HR+ subgroup after extending the neoadjuvant period to 24 weeks and such near-pCRs were less frequent in their HR− subgroup, one may conclude that HR+ HER2+ tumors need a longer duration of targeted therapy for optimal results. Moreover, such near-pCRs may be one of the reasons that pCR is not such a strong prognostic factor in HR+ HER2+ disease. The ADAPT HER2+/HR− sub-trial showed a substantial pCR rate of 90% for 12 weeks of paclitaxel plus dual antibody blockade with trastuzumab and pertuzumab.[13] Since pCR in the comparator arm with dual antibody blockade alone was only about one-third of that in the paclitaxel arm, one may conclude from ADAPT HER2+/HR− that the HR− subgroup is quite chemo-sensitive, but that de-escalation of chemotherapy is feasible. In order to evaluate the role of chemotherapy *versus* endocrine therapy with optimal anti-HER2 therapy, the ADAPT HER2+/HR+ follow-up trial TP II (Triple Positive II) [ClinicalTrials.gov identifier: NCT03272477] administers (again for 12 weeks) dual antibody blockade with trastuzumab and pertuzumab together with weekly paclitaxel or endocrine therapy. In the case of pCR, further adjuvant chemotherapy is optional in both arms while dual HER2 blockade will be continued in the adjuvant setting.

Given the excellent outcome with current treatment regimens in HER2+ EBC, any strategy changes need to be substantiated by evidence from prospective clinical trials. Even though treatment de-escalation or escalation may be warranted for individual patients or patient subgroups, one needs to be careful not to throw out the baby with the bathwater. Thus, at present, we do not have sufficient evidence to adjust neoadjuvant therapy in HER2+ EBC according to HR+ status in clinical routine. In particular, we do not have long-term outcome data at present from the early de-escalation trials in order to make definitive statements on the long-term impact of these modern therapy strategies.

Yet, for upcoming trials aiming at de-escalating or escalating therapy in HER2+ EBC, tumor biology, and in particular HR status, need to be taken into account. Moreover, since recent trials aiming to escalate targeted therapy in HER2+ EBC such as ALTTO[14] and APHINITY[9] have shown rather small efficacy differences in the HR+ subgroup, future trial designs (i.e. power calculations for survival endpoints, sample size capping for specific risk groups, follow-up time) also need to consider HR status in order to obtain clinically meaningful results.

Finally, in view of upcoming important trial results such as outcome data from KATHERINE [ClinicalTrials.gov identifier: NCT01772472] and ADAPT [ClinicalTrials.gov identifier: NCT01779206], systemic therapy concepts for HER2+ EBC may undergo substantial modification. Systemic therapy will be viewed as a continuum independent of whether it was started in the neoadjuvant or adjuvant setting. Neoadjuvant therapy will most likely remain a standard backbone as an initial *in vivo* response test, and its efficacy (pCR *versus* non-pCR) will serve as vital information for personalizing subsequent therapy choices.

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