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Viewpoints and debate

Is trastuzumab as a single agent obsolete in early breast cancer? No

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ABSTRACT

Until very recently, the "one size fits all" approach, with trastuzumab and chemotherapy with or without endocrine therapy, has been considered standard of care in almost all patients with HER2-positive early breast cancer. The combination of trastuzumab and chemotherapy is considered an undeniable therapy in this setting, given the unquestionable clinical benefit and the favorable safety profile. This almost universal adoption of trastuzumab-based therapies in early breast cancer has led to a proportional increase of overtreated patients, thus making treatment de-escalation in HER2-positive early breast cancer one of the major and more urgent unmet clinical need. In patients with HER2-positive disease at low/intermediate risk, single agent trastuzumab is not at all obsolete, and actually it remains the standard of care and represents the basis for many current efforts to a tailored treatment de-escalation. In this population, it is now crucial to improve treatment tailoring, by fine-tuning both patient selection and treatment administration.

1. Text

The "one size fits all" approach of trastuzumab given with chemotherapy and continued thereafter up to one year with or without endocrine therapy is the standard of care in almost all patients with HER2-positive early breast cancer, unless specific contraindications exist [1]. The combination of trastuzumab and chemotherapy is viewed as a "must do" given the unquestionable clinical benefit and the favorable safety profile. Such a treatment is also recommended in patients with tumors at lower risk of recurrence (T1a-bN0), despite the lack of evidence from randomized trials [1]. The risk of recurrence in this subgroup is relatively small but, due to the aggressive biological behavior of the disease, [2,3] the proportional benefit provided by adjuvant trastuzumab seems independent of tumor size and nodal status [4].

The almost universal adoption of trastuzumab-based therapies in early breast cancer has led to a proportional increase of overtreated patients. Hence, the goal of treatment de-escalation in HER2-positive early breast cancer is justified and its pursue is timely. The non-randomized APT trial has addressed this clinical question with a remarkably innovative approach. APT included patients with small (91.1% $\leq$ 2 cm), node negative HER2-positive tumors, and showed that the outcome remains excellent in women with such tumor presentation even if anthracycline administration were omitted [5]. Interestingly, this trial did not aim to demonstrate the non-inferiority of this treatment strategy compared to a standard anthracycline-containing regimen, which would have likely been superior. The innovative goal of the study was to show that the "residual risk of recurrence" is still very low with a de-escalated treatment. Therefore, adding drugs on this regimen might be statistically better, but it would not be worthy in terms of cost/efficacy balance and toxicity.

Other attempts to treatment de-escalation have investigated shorter durations of trastuzumab therapy. Some trials have explored this strategy in patients at any risk of recurrence, with the aim of demonstrating the "non-inferiority" [6,7]. None of the trials adopting trastuzumab for shorter than 1 year demonstrated non-inferiority, and the indication of trastuzumab for one year remains the standard of care. However, such an approach might be reconsidered and evaluated specifically in patients with HER2-positive disease at lower risk of recurrence, as – in this subgroup - the outcome is good enough to justify a less intensive treatment.

In patients with low-risk HER2-positive disease, single agent trastuzumab is not obsolete, but represents the backbone therapy for many current efforts to a tailored treatment de-escalation (Fig. 1).

In high-risk HER2-positive disease, a clinically meaningful proportion of patients will relapse and eventually die despite the best trastuzumab single agent regimen. Dual HER2 blockade is a therapeutic approach superior to anti-HER2 monotherapy. Different dual HER2-blockade strategies have been evaluated in the

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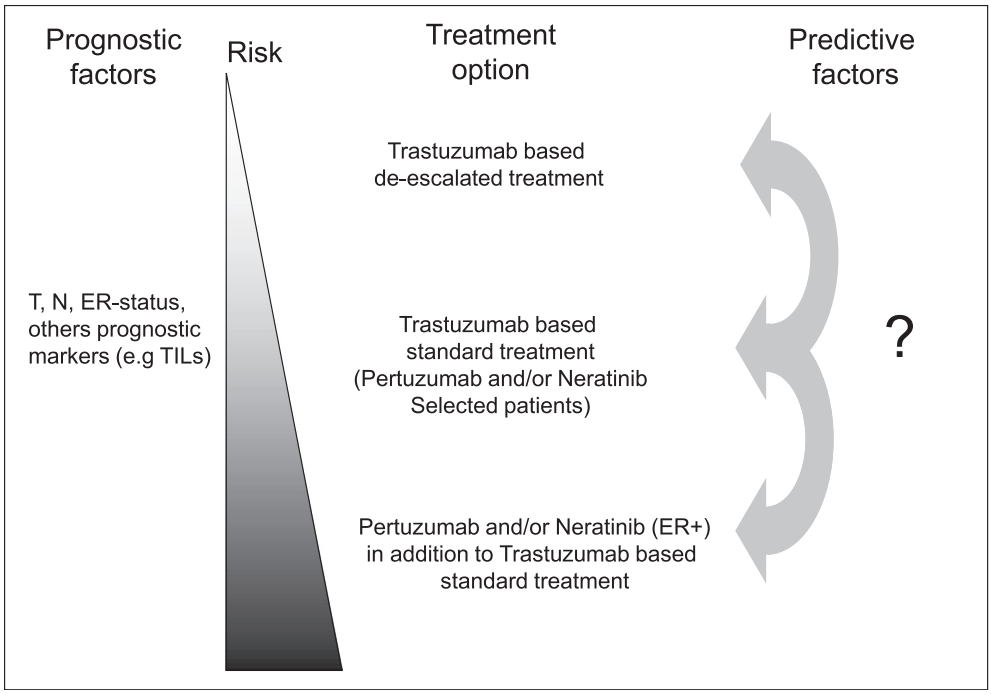

Fig. 1. Treatment options in HER2-positive early breast cancer with current and possibly future criteria of treatment selection. (TILs, Tumor Infiltrating Lymphocytes).

neoadjuvant setting (e.g. NeoALTTO [8] and NeoSphere [9] trials), with a significant improvement in pCR rate as compared to trastuzumab single agent [10]. The positive results of the NeoSphere study, which tested the addition of pertuzumab to trastuzumab concurrently to docetaxel, [11,12] led both FDA and EMA to the accelerated approval of neoadjuvant pertuzumab. These encouraging results supported the design of two phase III adjuvant randomized trials, ALTTO [13] and APHINITY [14], which tested the combination of lapatinib/trastuzumab and pertuzumab/trastuzumab, respectively. The design of the two trials are considerably different, as well as the results, but they have two relevant common features. First, they were both designed according to the principle of "one size fits all" and the logic of an "add-on" strategy, whereby the average improvement provided by the addition of a new drug cannot be negated to any patient with the average characteristics that fit the indication. The ALTTO trial enrolled all HER2-positive patients with a tumor of at least 1 cm (T1c), regardless of nodal status. The APHINITY trial enrolled also patients with tumors between 0.5 and 1.0 cm and node-negative status, provided they had at least one of the following features: histologic or nuclear grade 3, ER-negative or age younger than 35 years. In both trials, around 40% of the whole population was pT1 and/or node-negative. Furthermore, in both trials the number of events was much lower than expected, thus significantly affecting the statistical assumption and the statistical power. It is therefore prudent to interpret the results of both studies with caution at this time.

The two trials generated different results. The ALTTO trial was negative according to the pre-specified statistical threshold [13]. In particular, the trial included also patients treated with sequential anti-HER2 therapy, which is now considered inferior to concurrent administration [15]. At an updated follow-up analysis, considering only the concurrent arm, lapatinib and trastuzumab combination was not superior to trastuzumab single agent (HR 0.92, CI 95% (0.72–1.18); $p = 0.536$) [16]. The APHINITY trial instead was a statistically positive study. The addition of pertuzumab to trastuzumab reduced the risk of invasive-disease events - the primary endpoint of the study - (HR 0.81, CI 95% 0.66–1.00; $p = 0.045$). Given the excellent outcome with single agent trastuzumab (93.2% 3-year rate of invasive-DFS), the absolute risk reduction of 0.9% in the intent-to-treat population, corresponding to a number needed to treat (NNT) of 111, was statistically significant, but of questionable clinical meaning, and unlikely cost effective. In brief, the addition of pertuzumab in a "one-size-fits all" manner to all HER2-positive early breast cancer patients statistically improved outcome, but it does not seem to be worth the cost and the toxicity in all cases. For this reason, the FDA and the EMA approved the use of adjuvant pertuzumab only for patients with HER2-positive early breast cancer at "high risk of recurrence". Therefore, single agent trastuzumab in combination with chemotherapy is still the standard of care for patients with breast cancer at low/intermediate-risk (Fig. 1).

In appraising the efficacy results of a given treatment, we have to take into account the statistical significance (p value), the magnitude of the effect size, and its clinical relevance. The effect size can be estimated by relative (e.g. Hazard Ratio) and absolute (e.g. percentage of absolute risk reduction, NNT) measurements. In the APHYNITY trial, there is no evidence that the relative effect size is different in any of the defined subgroups, and interaction tests were not statistically significant. The finding is consistent with the benefit of adding trastuzumab alone to chemotherapy, a benefit which is independent of tumor size, nodal status and estrogen-receptor status [17]. The clinical relevance is instead more linked to the absolute effect size, which depends on the relative risk reduction as well as on the actual probability of the events occurring ("residual" risk of recurrence taking into account other treatments). For this reason, FDA and EMA, decided to restrict the indication to patients at high-risk of recurrence "such as those with hormone-receptor negative or those with node-positive breast cancer" (Fig. 1). These two subgroups have indeed a higher risk of recurrence and apparently derive a more relevant absolute clinical benefit (at 4-years, 2.3% in ER-negative and 3.2% in node-positive). However, these subgroups are far to be homogeneous with respect

to the individual patient risk. For instance, at 3-years, in the node-positive group, the absolute clinical benefit was 1.1% in the 1–3 node-positive group and 2.8% in the group with at least 4 positive nodes. Additionally, T and N provide independent prognostic information, and risk is a continuous – and not a categorical – function (Fig. 1). With such a strict definition of "high-risk" population, some node negative patients at substantial risk of relapse may eventually be denied an effective treatment. For example, using the Predict tool v2.1 to estimate the individual risk of death at 15 years, a patient with pT1b (1 cm) pN1 (1 positive node) ER-negative tumor and a patient with a pT2 (4.0 cm) pN0 ER-positive tumor would have similar risk of death when treated with trastuzumab, chemotherapy ± endocrine treatment, but only the first woman would be entitled to adjuvant pertuzumab according to the current approval [18].

An important caveat in this discussion is that the APHYNITY trial is still immature, with a median follow-up of only 45 months. The absolute benefit in the intent-to-treat population seems to almost double from 3 to 4 years (0.9% and 1.7%, respectively). A longer follow-up is needed to properly estimate the actual magnitude of pertuzumab benefit. Also, the interpretation of these early results by ER-status requires caution, as for trastuzumab - in the lower risk population - the proportional benefit was similar, although timing of relapses and absolute magnitude of benefit seemed to differ over time [4]. Finally, Aphinity was amended at mid-enrollment with the purpose to "enrich" the trial with patients at higher risk of relapse. The different risk of the two cohorts has generated a time-dependent unbalance that would ask to wait for longer follow-up before a more sounder interpretation of the results.

The ExteNET [19] trial tested one year of therapy with Neratinib, after the end of adjuvant trastuzumab. The conduct of the trial has raised some major concerns, mainly due to the three global amendments to the study design and the statistical plan that occurred each time the drug was sold to a new company. This is one of the reasons for missing from the analysis 24% of the enrolled cases, since patients had to be re-consented at each amendment. At a median follow-up of 5.2 years, the study demonstrated a statistically significant risk-reduction form neratinib, which seemed to be limited to ER-positive tumors (5-year absolute benefit of 4.4% and −0.1% in ER+ and ER-, respectively). The finding is consistent with the ability of neratinib to effectively modulate the crosstalk between the ER and HER2 pathways [20]. All the previous considerations about the residual risk of recurrence and the need to consider the actual absolute benefit apply also to Neratinib, with the additional caution related to the safety profile of the drug, especially G3 diarrhea, which occurred in 40% of patients; loperamide prophylaxis reduces the rate to about 0–17%.

Trastuzumab-single agent based therapies remain the standard of care for patients with HER2-positive early breast cancer at low/intermediate risk. However, there is an urgent clinical need to improve treatment tailoring, which only can be the basis for de-escalation, because it is crucial to offer the maximum chance of cure to whom is really in need, but it also is ever more important to guide a rational and personalized de-escalation in patients at lower risk of relapse. Cost-effectiveness and financial toxicity should also be taken into account in treatment decision. Optimal treatment selection is again the most effective way to overcome the financial hurdles related to the introduction of new drugs. In order to achieve this goal, it is paramount to develop more precise context-specific prognostic factors, and identify those patients with residual risk of recurrence, who may benefit by additional therapies [21]. In addition, predictive factors are needed to early identify those patients, who will derive the greatest benefit from a given treatment, as well as those who will not derive benefit [22] (Fig. 1). This will ultimately improve cost/effectiveness not only by simply cutting costs, but also – and more importantly - by fine-tuning patient selection, and adapting treatment administration.

Conflicts of interest

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