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Viewpoints and debate

Pathologic response at the epicenter of the treatment decision-making process in Human Epidermal Receptor–Type 2 overexpressing (Her2+) Early Breast Cancer (EBC): Challenges and opportunities for financially-constrained healthcare systems

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ABSTRACT

After more than two decades of intensive research, tremendous progress has been achieved in the management of Human Epidermal Receptor-2 overexpressing (Her2+) Early Breast Cancer (EBC). In the latest years, major clinical trials have explored the neoadjuvant scenario, in addition to the prognostic role of pathologic complete response (pCR) and the possibility of a 'tumor biology-driven' patient selection provided by the assessment pathologic response. However, the introduction of new agents has been a major burden for financially-constrained healthcare systems—which includes those from most emerging markets (currently representing 85% of the world population) but also, to some extent, public systems from welfare states. This manuscript addresses evidence-based opportunities to promote a more rational utilization of the available resources in Her2+ EBC, in addition to areas of interest for future research in cost-efficiency.

In Early Breast Cancer (EBC), due to the speediness of the results and the possibility of an accelerated approval in some countries, pharmaceutical companies and independent research groups have invested heavily the neoadjuvant setting [1]. However, neoadjuvant trials have usually been backed by larger adjuvant studies, which remain important for the permanent approval process [2].

Although the disease stage at presentation still matters [3–6], the achievement of a pathologic complete response (pCR) has been considered a powerful prognostic factor in Human Epidermal Receptor-2 overexpressing (Her2+) EBC [7–9]. In NEOSPHERE (NCT00545688), a randomized phase II trial, pertuzumab added to docetaxel and trastuzumab increased pCR rates in 15,8% points [10]. This data eventually led to pertuzumab's accelerated approval for Her2+ EBC measuring >2 cm or node-positive (N+) [11] – probably also influenced by practice-changing data produced in the metastatic setting [12]. Confirmatory data came from the APHINITY (NCT01358877) adjuvant trial [13,14], which eventually led to pertuzumab's regular approval in Her + EBC [15].

KATHERINE (NCT01772472) was a phase III trial in which patients with Her2+ EBC measuring more or equal to 1 cm or N+ who failed to achieve pCR after a standard neoadjuvant chemotherapy (NAC) and trastuzumab-based anti-Her2 therapy (dual-blockade in less than 20%) were randomized to receive 14 cycles of standard adjuvant trastuzumab or trastuzumab emtansine (T-DM1). The released interim results disclosed a robust 50% reduction in the risk of an IDFS event (HR, 0.50; 95% CI, 0.39 to 0.64; $P < 0.001$; 3-year IDFS 77% vs. 88,3%) [16], and subgroup analyses indicated consistent benefits across all subgroups [16,17]. T-DM1 was associated with increased toxicity (grade ≥3 adverse events [AEs], 25,7% vs. 15,4%; AEs leading to discontinuation, 18% vs. 2,1%) [16] and, potentially, higher costs [18]. Of interest, only 71,4% of the patients completed the 14 cycles (and 21,8% received less than 11 cycles), mostly due to the emergence of AEs [16]. Patients treated with de-escalated NAC (e.g. 12 weeks of paclitaxel) were unfortunately not represented in KATHERINE.

By exploring the neoadjuvant model and the prognostic role of pCR, NEOSPHERE [4,10] and KATHERINE [16], respectively, have changed the landscape of Her2+ EBC management by leading, for instance, to a likely increase in the use of neoadjuvant therapy

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(aiming at the higher pCR rate [10] and the identification of trastuzumab-resistant cancers potentially 'rescuable' by T-DM1 [12]), to a greater awareness of the importance of a meticulous loco-regional staging [19,20] and of team members' compliance with multidisciplinary case discussion policies [21] – both aiming at identifying a greater number of suitable candidates for neo-adjuvant therapy.

In addition to efficacy and safety, cost-effectiveness is another important factor for policy-makers when considering new incorporations. Based on the aforementioned data, the following considerations can be made:

1. Considering that, in the pivotal APHINITY trial, the benefit from adjuvant dual-blockade was clearly restricted to N+ patients [14], it is currently unclear if neoadjuvant pertuzumab should be given to all cancers ≥ T2. In addition to deriving no significant benefit from pertuzumab in terms of IDFS [14], N0 patients treated with this agent are more likely to achieve a pCR and, consequently, less likely to be eligible for post-neoadjuvant T-DM1 – which has proven and substantial benefits in this population [16]. Therefore, provided N0 patients have undergone a meticulous loco-regional staging (Fig. 1), most will be adequately treated with neoadjuvant CT and trastuzumab – with lower costs and toxicity.
2. This rationale is in a way reinforced by the results of the KATHERINE trial [16], in which the benefit from T-DM1 was independent of the type of Her2 blockade and, despite a low use of dual-blockade, 'T-DM1-rescued' patients did well, with a 3-year IDFS close to 90% in the overall study population (and greater than 90% in selected subgroups—such as cT1, cT2, cN0 or HR+, according to subgroup analyses) [16].
3. According to KATHERINE trial subgroup analyses, potential exceptions to the aforementioned strategy are subgroups of patients identified as having high risk of recurrence despite being treated with T-DM1, such as mutually exclusive cohorts of patients with initially 'inoperable' or 'operable/HR−/N+' disease, who presented a greater than 20% risk of an IDFS event at 3 years; this probably also applies to patients with initial cT3-4 or cN + disease, who presented a 3-year IDFS below 90% despite being treated with T-DM1 [16].
4. The fact that almost 30% of the patients failed to complete the 14 cycles of T-DM1 [16] in the KATHERINE trial implies that the chosen treatment duration is potentially too long. Interestingly, similar data emerged in a recent trial of single agent adjuvant T-DM1 for 'low-risk' Her2+ EBC, in which 17% of the patients failed to complete the 17 cycles and, despite that, a very low recurrence rate (<5%) was reported [22]. Furthermore, the initial assumption that 17 cycles of T-DM1 would be better tolerated than the TH regimen (12 weeks of paclitaxel with concurrent followed by sequential trastuzumab for up to 52 weeks [23]) yielded conflicting conclusions [22,24].
5. In the KATHERINE trial, prior treatment with an anthracycline (AC) was associated with a lower use of dual-blockade (10% vs. 45% for non-AC CT) and resulted in lower toxicity in general (grade ≥3 AEs, 21,7% vs. 39,9% with non-AC based CT). Both AC and non-AC groups presented excellent outcomes and derived similar benefits from T-DM1 [17]. Therefore, it can be speculated that the use of AC-based NAC might directly reduce spending with anti-Her2 monoclonal antibodies and, indirectly, with management of AEs. Of interest, in the large PERSEPHONE trial, the equivalent efficacy of only 6 months of adjuvant trastuzumab was also better demonstrated in AC-treated patients [25]. Finally, concerns about the cardiac safety of AC-based CT are often raised. However, in both KATHERINE and APHINITY, approximately ¾ of the patients were treated with AC and, with appropriate patient selection (as per stringent inclusion criteria used in these trials), no evidence of clinically meaningful increases in cardiac toxicity has emerged so far [13,17] (a lower cumulative dose of AC might also contribute to this goal).
6. In the KATHERINE trial, the addition of a platinum compound – whose role in Her2+ BC remains unclear [26,27] – represented a further burden in terms of toxicity [28]. Clinical experience has also shown a significant increase in severe anemia which might lead to higher rates of blood transfusions [29–31] – all potentially affecting the cost-effectiveness of platin-based regimens in this setting [18].

Current gaps of information and potential opportunities for further research in Her2+ EBC include the following (see also in Fig. 1)

1. Would post-neoadjuvant T-DM1 also be effective in 'rescuing' non-pCR patients treated with 'de-escalated' neoadjuvant regimens, such as 12 weeks of paclitaxel [23,32], or endocrine therapy plus dual-blockade without CT (in Her2+/HR + EBC)? [33–35].
2. Could the treatment duration of post-neoadjuvant T-DM1 be shortened – especially in the lowest risk subgroups?
3. Although designing such a clinical trial would be statistically challenging, could 'low-risk' pCR patients (initial stage I-II and N−) be potential candidates for a 'no further treatment' strategy? [36].
4. Could 'high-risk' pCR patients [4–6] also benefit from post-neoadjuvant T-DM1?

For financially-constrained healthcare systems, a rational utilization of the resources may a matter of life or death. At the same time, considering the current high cure rates of Her2+ EBC, and the devastating personal and financial consequences of a metastatic recurrence, treatment rationalization measures must be pursued under a very tight level of responsibility and technical rationale. Based on the NEOSPHERE, APHINITY and KATHERINE trials data [4,10,13,14,16,17], the following set considerations can be made (Fig. 1):

1. Policy-makers should require evidence that Her2+ EBC cases have been discussed in a Multidisciplinary Tumor Board [21].
2. Most patients with Her2+ cancers cT1a–b/N0/any HR status, cT1c/N0/HR+, or elderly/frail patients with tumors of <3 cm/N0/any HR status will be adequately treated with upfront surgery followed by de-escalated adjuvant therapy (TH) [23].
3. Patients with cT1c N0 disease represent a particular challenge. On the one hand, they have been shown to do well with surgery followed by adjuvant TH in the APT trial [23]; on the other hand, they also appeared to derive benefit from T-DM1 in an exploratory analysis of the KATHERINE trial (0 vs. 6[18%] IDFS events; n = 77) [17]. For this particular subgroup, young age and HR− status (both underrepresented in the APT trial [23]) are two factors to be considered in the decision-making process.
4. Patients with cT2 N0 are candidates to neoadjuvant therapy (suggested schedule: AC-based CT → taxane plus concurrent trastuzumab; a schedule containing 6 cycles of chemotherapy in total might be appropriate and cost-efficient) [37–40]. There is currently no clear indication for dual-blockade in this population.
5. Patients with N+ or T3-4 cancers are candidates for NAC (as above) and dual-blockade.
6. Elderly or frail patients with a clear indication for neoadjuvant therapy can be treated with 12 weeks of paclitaxel plus anti-Her2 therapy provided they have a good cardiac function.

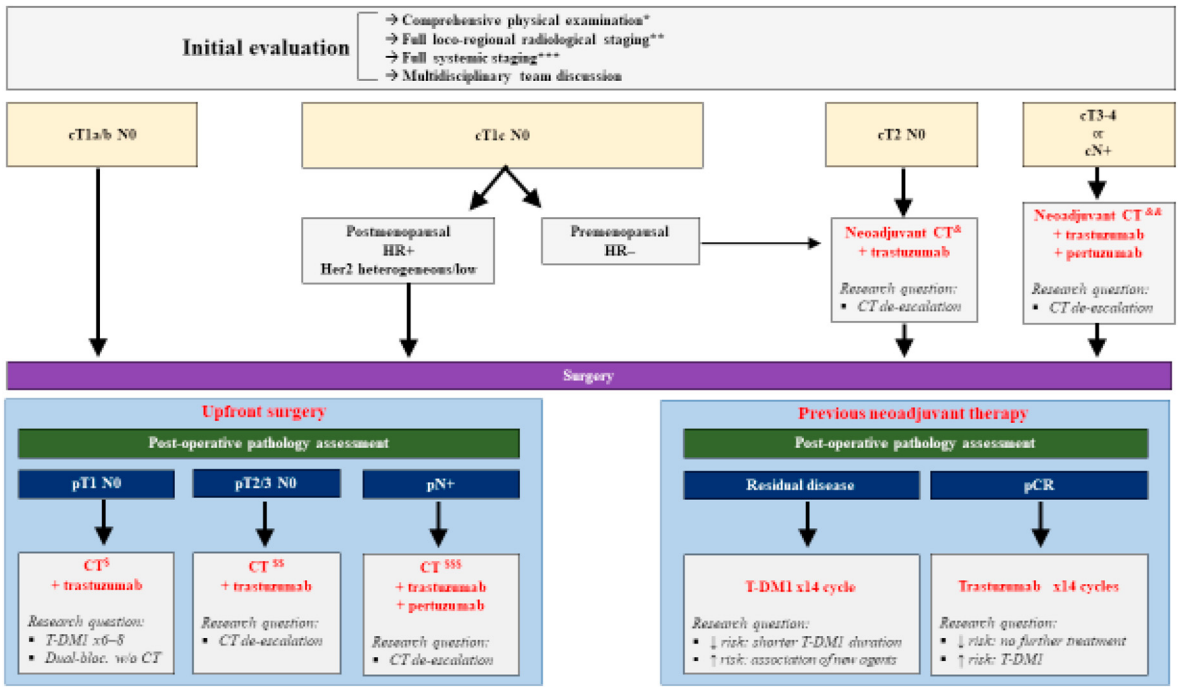

Fig. 1. Management of Her2+ EBC in financially-constrained healthcare systems and Most Relevant Research Questions for Each Situation.
* Performed by at least 2 specialists (oncologist and surgeon).
** Ideally with mammogram, breast and axillary ultrasonography (with additional biopsies/fine needle aspiration as required) and MRI.
*** PET-CT or bone scan plus CT scans of the chest and abdomen.
[&] Anthracycline or non-anthracycline-based (suggested regimen: [epi]doxorubicin + cyclophosphamide x3 cycles → Docetaxel 75–80mg/m2 ×3 cycles + trastuzumab x3-4 cycles.
[&&] Anthracycline or non-anthracycline-based (suggested regimen: [epi]doxorubicin + cyclophosphamide x3 cycles → Docetaxel 75mg/m2 ×3 cycles + trastuzumab x3-4 cycles + pertuzumab x3-4 cycles.
[$] APT trial schedule.
[$$] Anthracycline or non-anthracycline-based (suggested regimen: [epi]doxorubicin + cyclophosphamide x3 → Docetaxel 75–80mg/m2 ×3 cycles + trastuzumab→ trastuzumab for up to 52 weeks).
[$$$] Anthracycline or non-anthracycline-based (suggested regimen: [epi]doxorubicin + cyclophosphamide x3 → Docetaxel 75mg/m2 ×3 cycles + trastuzumab + pertuzumab → trastuzumab + pertuzumab for up to 52 weeks).
HR+ = hormonal-receptor positive; HR− = hormonal-receptor negative; N0 = node-negative; N+ = node-positive; CT scans = computed tomography; CT = chemotherapy; pCR = pathological complete response; T-DM1 = trastusumab emtansine; Pert. = pertuzumab; Dual-bloc = dual-blockade; w/o = without.

7. Patients who failed to achieve pCR are candidates for post-neoadjuvant T-DM1 for 14 cycles [16].

In conclusion, the advances achieved with the development of Her2-targeted therapies over the past 15 years have shaped the current landscape of Her2+ EBC management. Cure rates have achieved remarkably high rates, even for locally-advanced disease. However, gaining access to these costly technologies has been a challenge for financially-constrained healthcare systems, especially during the patent protection period. The recent availability of more cost-efficient trastuzumab biosimilars is good news and will hopefully allow researchers to fully concentrate on pertuzumab, T-DM1 and CT de-escalation. This manuscript addresses evidence-based opportunities to promote a more rational utilization of the resources, in addition to areas of interest for future research in cost-efficiency.

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