The Breast xxx (2017) 1–5

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Neoadjuvant therapy for triple negative and HER2-positive early breast cancer

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ARTICLE INFO

Article history:
Available online xxx

Keywords:
Carboplatin
Dual blockade
Early breast cancer
Neoadjuvant therapy

ABSTRACT

Today, neoadjuvant therapy can be considered a therapy standard in triple negative (TNBC) and in HER2-positive (HER2+) (particularly in HER2+ HR-) early breast cancer (EBC). Patients with a pathological complete response (pCR) will have a very favorable outcome. In TNBC, chemotherapy with anthracyclines and taxanes is standard. Data regarding addition of bevacizumab are rather heterogeneous. Addition of carboplatin improves pCR rates independent of BRCA status; whether this will translate into a survival benefit is still unclear. In HER2-positive (HER2+) disease, anti-HER2 antibody therapy with trastuzumab is given together with chemotherapy. For patients at high risk of relapse, dual HER2 blockade with trastuzumab and pertuzumab is standard. The chemotherapy backbone consists either of an anthracycline-taxane sequence or of an anthracycline-free regimen such as docetaxel and carboplatin. pCR rates depend on hormone receptor (HR) status. Anti-HER2 therapy is completed after surgery with trastuzumab for a total of one year. Future research needs to focus on avoiding overtreatment in patients with pCR (de-escalation) as well as on improved therapy options (escalation) for patients with non-pCR after standard neoadjuvant therapy. Here, early response markers (e.g. biomarkers, molecular imaging) as well as novel targeted agents may play an important role in the future.

1. Introduction

The concept of neoadjuvant therapy for early breast cancer (EBC) without distant metastases has substantially changed over the last two decades. Starting as preoperative chemotherapy in large inoperable tumors [1], it has now become a standard treatment option for certain EBC subtypes almost independent of tumor size – at least in tumors > 1 cm [2,3]. Next to enabling less aggressive surgery and more breast conserving therapy by reducing the local tumor burden in breast and axilla, neoadjuvant therapy also serves as an *in vivo* sensitivity test for the applied therapy. This may help to guide therapy but – if good clinical response is seen - may also motivate patients to finish their therapy as originally intended. Moreover, in case of non-pCR, subsequent treatment escalation may be possible in clinical trials as well as in routine care. (see Table 1)

Neoadjuvant chemotherapy is always indicated in cases where adjuvant chemotherapy would be indicated as well, such as in triple-negative (TNBC) and HER2+ disease; if chemotherapy was not indicated in the adjuvant setting because of favorable tumor biology, it should not be used as a neoadjuvant approach merely to reduce tumor size. Achievement of pCR at time of surgery is correlated with favorable patient outcome in all breast cancer subtypes [4]. Particularly in TNBC and HER2+ disease, pCR is associated with a much better overall outcome compared to non-pCR as also demonstrated by a FDA meta-analysis in over 12,000 patients. In HER2+ EBC, this association is particularly true for hormone-receptor negative (HR-) tumors [5].

Given these strong arguments for a neoadjuvant approach, particularly in TNBC and HER2+ disease, the times of immediate removal of a newly diagnosed breast cancer before all information is available should be over. Treatment concepts in EBC can only be finalized when HER2 and HR status are available in order to find the most appropriate therapeutic approach for an individual patient.

This article reviews the history of the neoadjuvant approach in TNBC and HER2+ EBC focusing on the evolution of therapy standards.

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http://dx.doi.org/10.1016/j.breast.2017.06.038
0960-9776/

Table 1
Clinical trials assessing the impact of carboplatin in neoadjuvant therapy of TNBC.

Trials (all phase II)	Patient number	TNBC definition	Therapy arms	pCR rates (platinum vs. control arm)	Significance	Reference
GEICAM 2006/03	94	basal-like (IHC): ER-, PR-, HER2- and cytokeratin 5/6 + or EGFR+	4x EC, then 4xDOC q3w + carboplatin AUC6 q3w	30% vs. 35% (pCR breast)	P = 0.61 (n.s.)	Alba et al. [16]
Japanese phase II trial	TNBC: n = 75	Immuno-histochemistry ER, PR, HER2	4x carboplatin AUC5 q21 + paclitaxel$_{80}$ weekly − 4xCEF (500/100/500) vs. P-CEF	61.2% vs. 26.3% (pCR breast)	P = 0.003 (subgroup analysis)	Ando et al. [15]
Geparsixto	TNBC: n = 315	ER and PR <1% HER2 negative	18x q1w: paclitaxel$_{80}$ + NPLD 20 mg/m^2 + carboplatin AUC2 (later 1.5)	53.2% vs. 36.9% (ypT0 ypN0)	P = 0.005 (planned subgroup analysis)	von Minckwitz et al., Lancet Oncology [13]
CALGB 40603 (Alliance)	443	ER and PR <10% HER2 negative	12x paclitaxel$_{80}$ weekly + carboplatin AUC6 q3w x4 − 4x ACq2w (+bevacizumab 10 mg/kg q2w)	60% vs. 44% (pCR breast)	P = 0.0018	Sikov et al., JCO [14]
WSG ADAPT TN	336	ER and PR <1% HER2 negative	Anthracycline-free: nab-paclitaxel 125 mg/m^2 + carboplatin AUC or gemcitabine 1000 mg/m^2 d1,8 q21 x4	45.9% vs. 28.7% (ypT0/is ypN0)	P < 0.001	Gluz et al. [22]

2. Triple negative disease

In TNBC, standard neoadjuvant therapy concepts using anthracyclines and taxanes achieve pCR rates (breast and axilla) over 30%. Liedtke et al. demonstrated for the first time that response to standard neoadjuvant chemotherapy predicts outcome in TNBC and that pCR correlates with excellent survival [6]. In order to improve outcome of patients with TNBC, several approaches for increasing the efficacy of neoadjvant chemotherapy have been pursued.

Addition of bevacizumab to a neoadjuvant anthracycline-taxane regimen increases pCR rates in HER2-negative EBC. In the GeparQuinto trial [7] and in the open-label ARTemis trial [8], the effect was mainly attributable to in TNBC whereas in the NSABP-B40 trial, HR + tumors benefitted most [9]. The observed pCR rate increase is consistent with the postulated anti-tumor effects of bevacizumab such as normalization of tumor vasculature and better delivery of chemotherapy to the tumor. In GeparQuinto, the pCR advantage did not translate into a survival advantage [10]. This is consistent with the BEATRICE trial where adjuvant bevacizumab did not improve patient survival in TNBC [11]. Yet, in NSABP-B40, addition of bevacizumab resulted in improved survival of patient with HR + disease: There was an increase in overall survival (HR 0.65; 95% CI 0.49–0.88; p = 0.004) but not in disease-free survival (HR 0.80; 0.63–1.01; p = 0.06) [12]. There are substantial differences between the individual trials regarding patient selection and therapy regimen that may have contributed to the discordant results. In NSABP B40 but not in GeparQuinto or ARTemis, patients received bevacizumab not just before but also after surgery for an additional 10 applications. This may have contributed to the survival impact as bevacizumab was able to affect both the primary tumor as well as dormant micrometastases.

The NSABP-B40 trial also demonstrated that adding capecitabine or gemcitabine to an anthracycline-taxane sequence does not improve pCR rates [9]. Nevertheless, addition of platinum to an anthracycline and taxane backbone improved pCR rates in TNBC in GeparSixto [13] and CALGB 40603 [14] as well as other smaller trials [15]. One trial did not see an improvement of pCR by adding carboplatin to an anthracycline-taxane sequence [16] (see Fig. 1). Even though pCR rates with carboplatin were highest in BRCA mutation carriers, the additional benefit from carboplatin was most visible in BRCA wildtype patients [17]. One explanation for this observation is that tumors in BRCA mutation carriers are very chemo-sensitive and the effect of the additional drug is therefore not as pronounced as in BRCA wildtype patients. The higher overall pCR rates in BRCA mutation carriers observed in GeparSixto certainly support this hypothesis. Nevertheless, the neoadjuvant data in TNBC so far do not support offering carboplatin only to BRCA mutation carriers.

Yet, whether this pCR advantage translates into a survival advantage is still under discussion. Whereas GeparSixto did see a significantly improved DFS [17], CALGB 40603 did not [18]. It remains unclear whether the different carboplatin schedules (weekly vs. q21) or the different anthracycline-taxane backbone (no alkalyting agent in GeparSixto) did contribute to these discordant survival data or whether the trials were simply underpowered to show a consistent transfer of the pCR advantage to a survival advantage. Nevertheless, considering all available evidence and the additional but manageable toxicity, addition of carboplatin to an anthracycline-taxane chemotherapy backbone should be offered to patients with TNBC if the clinical focus lies on achieving optimal pCR. Patients need to be informed, however, that it remains unclear whether a survival advantage can be expected by this intensification of their neoadjuvant therapy.

Using weekly nab-paclitaxel (125 mg/m^2) instead of paclitaxel (80 mg/m^2) significantly improved the pCR rate in GeparSepto, with the effect being most pronounced in the TNBC subset [19]. The recently presented ETNA trial, however, did not see a significant advantage of using weekly nab-paclitaxel (125 mg/m^2) in a 3/4 week schedule instead of paclitaxel weekly (90 mg/m^2) [20]. Nab-paclitaxel thus remains a valid option for neoadjuvant therapy in TNBC. As there is no approval for early breast cancer, its use seems to be limited to patients in whom paclitaxel or docetaxel cannot be given due to side effects or co-morbidities.

The WSG ADAPT umbrella trial [21] has recently shown that avoiding overtreatment and individualizing neoadjuvant therapy

Please cite this article in press as: Harbeck N, Gluz O, Neoadjuvant therapy for triple negative and HER2-positive early breast cancer, The Breast (2017), http://dx.doi.org/10.1016/j.breast.2017.06.038