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REVIEW ARTICLE

Recent Advances in the Neoadjuvant Treatment of Breast Cancer

Gábor Rubovszky, Zsolt Horváth[1]

Department of Medical Oncology and Clinical Pharmacology "B", National Institute of Oncology, Budapest; [1]Faculty of Medicine, Institute of Oncology, University of Debrecen, Debrecen, Hungary

In the last few decades, neoadjuvant therapy for breast cancer has gained considerable therapeutic importance. Despite extensive clinical investigations, it has not yet been clarified whether neoadjuvant therapy would result in improved survival in comparison with the standard adjuvant setting in any subgroups of patients with breast cancer. Chemotherapy is especially effective in the treatment of endocrine insensitive tumors, and such therapeutic benefit can be assumed for patients with triple-negative, or hormone receptor-negative and human epidermal growth factor receptor 2 (HER2)-positive breast cancer. However, dose escalation, modification of the therapeutic regimens according to early tumor response, as well as the optimal sequence of administration are still matters of debate. There is a current debate between clinical experts regarding the concomitant and sequential administration of carboplatin and capecitabine, respectively, as part of the standard neoadjuvant treatment, as well as the use of bevacizumab, as part of the preoperative treatment. In case of HER2 positive tumors, an anti-HER2 agent can be administered as part of the preoperative treatment, and according to preliminary clinical data, dual HER2 blockade can also be reasonable. Further, chemotherapy-free regimens can be justified in highly endocrine sensitive tumors, while immune modulating agents may also gain particular importance in the case of certain subtypes of breast cancer. Several small-molecule targeted therapies are under clinical investigation and are expected to provide new neoadjuvant treatment options. However, novel, more predictive biomarkers are required for further evaluation of the neoadjuvant therapies, as well as the effect of novel targeted agents intended to be incorporated into neoadjuvant therapy.

Key Words: *Antineoplastic agents, Breast neoplasms, Molecular targeted therapy, Neoadjuvant therapy*

INTRODUCTION

Adjuvant chemotherapy can improve disease outcome in early breast cancer; however, its appropriate method of application is still a matter of debate. In addition to the most commonly used anthracycline and taxane derivatives, other cytotoxic agents and targeted therapies can be administered. In the last few years, the preoperative introduction of chemotherapeutic regimens has become a general approach in the clinical practice [1]. The main purpose of the neoadjuvant therapy (NAT) is to reduce the size of the primary tumor, eventually allowing radical or more conservative surgical interventions [2]. NAT also allows an early evaluation of clinical efficacy; thus, changes in the applied chemotherapeutic regimen can be commenced at a relatively early stage [3]. The aim of this work is to collect relevant neoadjuvant trial results that may assist physicians to apply optimal treatment for patients with breast cancer.

CLINICAL RELEVANCE OF PATHOLOGICAL COMPLETE RESPONSE

Early randomized trials comparing NAT with adjuvant chemotherapy failed to detect any improvement in overall survival (OS) rates [4]. On the other hand, clinical trial data have suggested that pathological complete response (pCR) observed after NAT, may result in higher survival rates. However, it should be pointed out that in these early trials, the definition of pCR was inconsistent. In line with the currently accepted definition, pCR denotes a condition when residual tumor is neither detected in the breast, nor in the axilla. However, according to several investigators, *in-situ* remnant in the breast is acceptable.

In the meta-analysis published by Cortazar et al. [5], a total number of 12 international controlled trials were evaluated, yielding a pooled population of 11,955 patients. This meta-analysis revealed that patients with pCR (ypT0/ypN0) had superior event-free survival (EFS) and OS. This prognostic cor-

Correspondence to: Gábor Rubovszky
Department of Medical Oncology and Clinical Pharmacology "B", National Institute of Oncology, Ráth György u.7-9, 1122 Budapest, Hungary
Tel: +36-1-2248600, Fax: +36-1-2248744
E-mail: garub@oncol.hu

relation was most prominent for patients who presented de-differentiated, triple-negative (TN), and human epidermal growth factor receptor 2 (HER2)-positive (HER2+) tumors; in case of HER2 positivity, trastuzumab therapy was administered. To assess the utility of pCR for neoadjuvant anti-HER2 therapies, Broglio et al. [6] performed a patient-level analysis on 38 trials with 5,768 patients that compared the EFS and OS hazard ratios in pCR and non-pCR patients. Patients with pCR had significantly longer EFS compared to non-pCR (hazard ratio, 0.37), and that was more pronounced in case of hormone receptor negativity (hazard ratio, 0.29) and after neoadjuvant anti-HER2 therapy (hazard ratio, 0.35). The same magnitude of positive effect of pCR was also observed after OS evaluation (hazard ratio, 0.34).

It has been claimed though, that the clinical evidence does not support pCR rate as an early predictor factor for OS. Although patients generally may expect a longer survival after pathological complete remission, in individual trials, pCR rate defined as a surrogate endpoint, may not predict survival [7]. Cortazar et al. [5], found no significant association between the frequency of pCR and survival data, when trials were separately analyzed.

In another meta-analysis published by Berruti et al. [8], data from 29 trials (14,641 patients, 59 arms and 30 comparisons) were evaluated. This study demonstrated a weak association of pCR rates with disease-free survival (DFS) and OS. This association, however, reached statistical significance when intensified dose-dense and standard-dose regimens were compared.

From a regulatory perspective, the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) acknowledged pCR as a surrogate endpoint in clinical trials performed as part of the development of new drug products in certain high-risk subgroups. In accordance therewith, the majority of the NAT trials defined pCR as a primary endpoint.

SUBGROUP DIFFERENCES IN NAT TRIALS

In general, the efficacy of NAT largely differs between subgroups of patients with different subtypes of breast cancer. Von Minckwitz et al. [9] reported a meta-analysis of seven NAT trials, yielding a pooled population of 6,377 patients. The main finding of this analysis was that patients' hormonal receptor (HR) and HER2 status profoundly influences pCR rate and survival, after demonstrating a higher pCR rate in HR-negative (HR−) tumors than in HR-positive (HR+) tumors. Moreover, the lowest pCR rate was found among patients with luminal A type tumors (6.4%), higher rate in luminal B type tumors (11%–22%), and a maximal pCR rate was observed in the groups of HER2+ and TN patients (27%–32%). In luminal

B type, HER2+ and TN tumors patients with pCR had significantly higher OS compared to other subtypes. These observations were also confirmed by the previously mentioned meta-analyses [5,6].

The TN breast cancer (TNBC) subgroup can be divided into smaller subgroups on the basis of genetic differences [10]. Gene expression analysis of 386 tumor samples has revealed 6 distinct subtypes of TNBC: two basal-like (BL1 and BL2), an immuno-modulatory (IM), a mesenchymal (M), a mesenchymal stem-like (MSL), and a luminal androgen receptor (LAR) subtype. Eleven of the analyzed TN tumor samples were reported as unclassified (UNC). According to the PAM50 classification, the BL1, BL2, IM, and M subtypes are largely basal-like, the MSL subtype is largely normal-like, and the LAR subtype is mostly comprised of luminal and HER subtypes [11].

The efficacy of anthracycline and taxane containing NAT differed between groups of patients with different tumor subtypes [12]. The highest pCR rate was found in BL1 (50%), and the lowest in BL2 and LAR (0%–10%) subgroups. The same analysis demonstrated that tumor-subtypes can provide a basis for different therapeutic approaches. The BL1, IM, and UNC subtypes are considered to be highly sensitive to genotoxic anticancer agents. Therefore, they can be treated with platinum-based chemotherapeutic regimens, as well as with poly ADP-ribose polymerase (PARP) inhibitors [12]. Even though, there is no clear association between the IM subtype and the presence of tumor infiltrating lymphocytes (TIL), gene expression data of immunological relevance show correlation with TILs [11]. Regarding the LAR subtypes, antiandrogen agents and phosphoinositide 3-kinase (PI3K) inhibitors can be used effectively due to the high PI3K catalytic subunit alpha (PIK3CA) mutation rate (40% vs. 4% in other subtypes). The M subtype was found to respond to the treatment with the SRC inhibitor dasatinib. Furthermore, PI3K-, protein kinase B (AKT)-, mammalian target of rapamycin (mTOR)-, mitogen-activated protein kinase kinase (MEK)-, cell cycle- and growth factor-inhibitors are also assumed to have therapeutic relevance in TNBC [10,12]. In HR+ and HER2-negative (HER2−) subgroups neoadjuvant chemotherapy is less effective. Although it may have role, especially in more advanced and high-grade tumors, targeted therapies, especially endocrine therapy (ET), are generally considered more essential.

NEOADJUVANT CHEMOTHERAPY: IMPACT OF DOSE, COMBINATION AND SEQUENCE

The majority of the relevant guidelines recommend the incorporation of anthracyclines and taxanes in NAT regimens targeted for breast cancer [13], but there is no agreement on

the optimal combination, dose, and sequence. In general, similar doses and combinations are used both in adjuvant and neoadjuvant settings. Anthracyclines and taxanes have been reported to be used both concomitantly and sequentially in controlled trials. In a phase III trial, similar efficacy of doxorubicin was observed when combined with either cyclophosphamide or docetaxel [14]. In the GEPARDUO trial, a number of 913 women with untreated operable breast cancer were randomized to receive either four cycles of doxorubicin-docetaxel combination, or four cycles of doxorubicin-cyclophosphamide and subsequently, four cycles of docetaxel. Although the subsequent administration of doxorubicin and docetaxel resulted in a significantly higher pCR rate (14.3%) compared to the concomitant administration thereof (7%), the authors attributed this effect to the longer duration of the sequential therapy [15]. In contrast, Vriens et al. [16] found that adding four cycles of docetaxel sequentially to four cycles of doxorubicin-cyclophosphamide does not significantly improve the pCR rate, while it causes higher rate of grade 3 to 4 sensory neuropathy (5% vs. 0%). Further, in the BCIRG-005 adjuvant trial, 3,298 patients were enrolled, and similar DFS and OS values were reported after concomitant and sequential therapy [17]. On the other hand, the NSABP B-30 trial showed slightly higher survival rates for sequential therapy [18]. Since trials failed to clearly demonstrate the superiority of either approach, both types of administration are accepted during NAT; though, most practitioners prefer sequential therapy.

It is also unclear whether dose-dense therapy is superior to conventional schemes or not. According to the National Comprehensive Cancer Network (NCCN) guidelines, the dose-dense therapy is preferred, although this approach is questioned by some experts [19]. In a recent meta-analysis published by Petrelli et al. [20], it was found that dose-dense therapy in a NAT setting resulted in a significantly higher pCR rate, but had no significant effect on DFS and OS [20]. Based on the meta-analysis of four adjuvant clinical trials enrolling 3,418 patients in total, Lemos Duarte et al. [21] have found that dose-dense therapy led to a significant improvement in DFS irrespective of HR status, but had no significant influence on OS. A more comprehensive meta-analysis of eight adjuvant trials, recruiting a total number of 17,188 adult women with resected BC, was subsequently published by Petrelli et al. [22]. This analysis concluded that dose-dense therapy was associated with significantly higher DFS and OS. However, only the HR negative subgroup showed a significant improvement regarding OS.

Although significant effect of dose-dense therapy was apparent only when it was adjuvantly applied, the meta-analyses reported similar hazard ratios for OS; 0.89 for the NAT [20]

and 0.86 for the adjuvant [22] therapy. This finding introduces the possible use of dose-dense regimes in the neoadjuvant setting, at least for patients with HR– tumors.

According to current therapeutic standards, the combination of doxorubicin or epirubicin and docetaxel or paclitaxel is highly recommended [14,23-26]. The exact therapeutic role of newly developed chemotherapeutic agents is still under investigation.

In the GEPARSIXTO trial, a pCR rate of 37% was observed in patients receiving liposomal doxorubicin plus paclitaxel in a weekly basis. Upon this result, the combination of liposomal doxorubicin and paclitaxel has become an alternative to anthracycline in NAT [27]. The phase III GEPARSEPTO trial reported the enrolment of 1,206 patients who were randomly assigned to receive either nab-paclitaxel or paclitaxel before epirubicin-cyclophosphamide treatment. Although, significantly higher pCR rate was observed in the nab-paclitaxel arm (38% vs. 29%, respectively), the rate of grade 3 to 4 sensory neuropathy was also higher in this group [28]. However, this finding failed to be endorsed by the ETNA trial, which enrolled 602 patients and found similar pCR rates in the nab-paclitaxel and paclitaxel arms [29]. It is noteworthy though, that in the ETNA trial, the introduction of anthracycline regimen was optional and depended on the decision of the treating physician, who could biased the overall conclusion on the efficacy of nab-paclitaxel. Nevertheless, the clear therapeutic benefit of nab-paclitaxel is still unclear. The results of the NEOTANGO trial have proven the superiority of the taxane-anthracycline sequence. In this 4-arm trial, the sequence of epirubicin-cyclophosphamide combination and paclitaxel, and the rationale of the add-on gemcitabine therapy were questioned. After a 47-month median follow-up of 831 patients, the pCR rate was significantly higher when NAT was started with paclitaxel, than with the epirubicin-cyclophosphamide combination (20% vs. 15%). The administration of gemcitabine had no influence on the pCR rate [30]. However, other studies found no evidence supporting that the order of administration of anthracyclines and taxanes would affect therapeutic outcome of HER2+ patients [31]. Bines et al. [32] analyzed the results provided by studies of adjuvant and neoadjuvant chemotherapeutic settings, and concluded that taxanes are more beneficial when administered at first. For this reason, they recommended its use in routine clinical practice.

ADAPTED STRATEGIES IN NAT

The revision of the applied NAT strategies on the basis of newly published evidence, is frequently driven by the intention to improve therapeutic effectiveness. The choice of ther-

apeutic strategies can be based on tumor characteristics, including HR and HER2 status, genetic subtypes, or alterations, as well as on early response evaluation, commonly via the response guided therapy. Even though the approach to adjust therapy according to early response seems logical in case of poorly or nonresponding patients, its routine use in the clinical practice has not yet been established.

The WSG-ADAPT is an ongoing "umbrella" trial in the frame of which, 4,936 patients are projected to enroll and assign in four subtrial groups (4,000 patients in HR+/HER2−, 380 patients in HR+/HER2+, 220 patients in HR−/HER2+, and 336 patients in TN subgroup). Subtrials focus on the identification of early surrogate markers for subgroup adapted therapy success in the neoadjuvant setting [33]. The main rationale of this study is substantiated by the clinical observation indicating that a part of HR+ tumors are good candidates for neoadjuvant chemotherapy, especially those with high-risk features, like advanced grade, high Ki-67 or HER2 positivity [34]. In contrast, well-differentiated HR+ tumors, especially those with lobular histology, are improbable to respond to chemotherapy and are good candidates for endocrine and other targeted therapies.

The GEPARTRIO trial investigated the DFS and OS after response-guided theory in patients with early breast cancer. A total number of 2,072 patients were enrolled and received two cycles of docetaxel-doxorubicin-cyclophosphamide (TAC). Patients considered as early responders (roughly 2/3 of patients) were randomized to receive an additional four or six cycles of TAC. Nonresponder subjects were randomized to four cycles of TAC or vinorelbine-capecitabine (NX) combination. Among early responders, eight cycles of TAC resulted in significantly higher OS compared to the OS after six cycles of TAC. This difference was most prominent among HR+ patients. In general, results proved the superiority of response-guided (8×TAC or TAC-NX) chemotherapy [35].

Response-guided therapy was also applied in the GEPAR-QUINTO trial. Patients with HER2− tumors were firstly randomized to receive four cycles of epirubicin-cyclophosph-amide with or without bevacizumab. Then, four cycles of docetaxel with or without bevacizumab were administered to patients with clinical response, while nonresponders received weekly paclitaxel 12 with or without everolimus. Although this study design did not allow the assessment of the benefit of the response-guided therapy, the application of this therapy as a recognized therapeutic approach, could be concluded from this trial setting [36].

In a trial conducted by Wang-Lopez et al. [37], a number of 264 previously untreated stage II–III operable patients with breast cancer were randomized to three cycles of 5-fluoroura-cil-epirubicin-cyclophosphamide combination (FEC), followed by three cycles of docetaxel, or to receive response-guided treatment. In the response-guided arm, the first evaluation occurred after two or four additional cycles of FEC. Patients with insufficient response (i.e., < 30% or < 50% tumor size decreases after two or four cycles of FEC, respectively) were switched to a total of four or two cycles of docetaxel. Patients with sufficient response received six cycles of FEC. No significant differences were found between study arms in terms of breast conserving surgery and pCR rates. These findings support that docetaxel can improve treatment efficacy, even in the case of relatively resistant tumors, while it remains unclear whether responders and nonresponders should be treated differently.

In order to explore the benefit of switching between different therapeutic regimens—adapting the treatment to the clinical situation—studies comprising a control arm, including patients treated conventionally irrespective of early tumor response seem more appropriate, since they allow for evaluation of the benefit of the alternative therapeutic approach. However, when comparing therapeutic regimens considered equally efficacious, the cross-over design is also a feasible alternative. As examples, PREDIX HER2 (NTC02568839) and PREDIX LUMB (NCT02603679) trials are cited. In both trials, after early disease evaluation, patients either remained in the same arm, or if no response was proven, they crossed over to the comparator arm.

In case of HR+ tumors, the role of chemotherapy in early setting is debated. In the WSG-ADAPT trial, patients with HR+/HER2− tumors were treated with ET for 3 months. Then, the low risk patients with good response were assigned to further ET, while the high-risk patients, showing poor response, received chemotherapy [33]. In ALTERNATE trial (NCT01953588), anastrozole, fulvestrant, or their combination were used during the 12-week induction period. Then, ET was either continued in patients responding to the induction phase, or therapy was switched to paclitaxel for a 12-week period.

ADDITIONAL CYCLES OVER STANDARD THERAPY

There is not enough evidence justifying the benefits of chemotherapies exceeding standard length. Therefore, current guidelines do not recommend extended chemotherapies, including those applied postoperatively. In the GEPARQUATTRO trial, the authors have concluded that longer therapy is not beneficial; however, lower doses of docetaxel were applied [38]. On the other hand, the GEPARTRIO trial has found that

chemotherapy administered over a prolonged period (i.e., 8×TAC vs. 6×TAC) is more efficacious [39].

In a pooled analysis of seven German neoadjuvant trials, higher pCR rate was associated with an increase in the number of chemotherapy cycles and cumulative doses of anthracyclines and taxanes, as well as with the add-on capecitabine and trastuzumab treatment. These observations, together with similar findings from other studies, indicated that more intensified neoadjuvant treatment could improve patients outcome, at least in selected cases [40].

Another example is the CREATE-X phase III adjuvant trial, where 455 HER2– patients with residual disease after NAT were randomized either to receive eight cycles of capecitabine, or no additional chemotherapy [41]. Capecitabine treatment resulted in significantly higher 5-year DFS and OS, compared to the control arm. This difference was the most pronounced in the TN subgroup. However, this approach needs to be further investigated, especially in patients with poor prognosis, such as patients with TN cancer showing non-pCR response.

INCORPORATING ADDITIONAL AGENTS INTO NAT REGIMENS

Dual blockade in HER2+ tumors

In case of HER2+ breast cancer treatment, the incorporation of trastuzumab into NAT resulted in higher pCR and better survival [8]. Although it has not yet been proven, it has been suggested that trastuzumab would be more efficacious when administered preoperatively than postoperatively. The evidences of a higher rate of pCR observed for trastuzumab containing combinations, and the more favorable results with early administration of trastuzumab, set the neoadjuvant trastuzumab as an accepted scenario. The optimal chemotherapy backbone was also questioned in several trials, but the strong additive effect of trastuzumab is generally accepted. Achieving dual HER2 receptor blockade by adding lapatinib or pertuzumab to trastuzumab, significantly increased pCR rate to 50% to 60%, as observed in relevant trials [42-47]. However, therapeutic benefit manifested mainly in case of HR– tumors [9,45]. These trials have not yet demonstrated whether the higher pCR rate would result in higher OS [40,42].

The results of the GEPARQUINTO [48] and CALGB 40601 [45] trials indicated that trastuzumab is more effective than lapatinib, whereas the NeoALTTO [44] and NSABP-B41 [47] trials reported no significant difference between lapatinib and trastuzumab treatments. Nevertheless, while approximately one third of patients discontinued lapatinib due to adverse events, the trastuzumab-pertuzumab combination is more ac-

cepted.

In the phase III NSABP B-52 study, 315 HR+ and HER2+ patients were randomized to be given docetaxel, carboplatin (CBP), trastuzumab, and pertuzumab with or without oestrogen deprivation therapy (aromatase inhibitor and luteinizing hormone-releasing hormone [LHRH] analogue if premenopausal). In the investigational arm, the pCR rate was not significantly higher (40.9% vs. 46.1%) along with similar toxicity profile, suggesting that ET is not important for dual HER2-blockade and chemotherapy [49].

Oral HER2 blockers are under clinical investigation. Early results obtained with pan-HER blocker afatinib and irreversible HER2 blocker neratinib indicated the therapeutic efficacy of these compounds. However, their superiority over lapatinib has not yet been established [50,51].

Chemo-free NAT or ET after NAT

The pCR rate in HR+ tumors is significantly lower compared to other subtypes. This finding raises the question whether chemo-free therapy is reasonable. In the phase II TBCRC006 trial, trastuzumab and lapatinib were combined either with letrozol or LHRH analogue, according to HR and menopausal status. Overall, the pCR rate was 21% for HR+ tumors [52], while pCR rates obtained for HR+ patients in the NeoSphere trial were lower for trastuzumab-pertuzumab combination (5.9%), similar for trastuzumab-docetaxel or pertuzumab-docetaxel combinations (17.4%–20%), and higher for trastuzumab-pertuzumab-docetaxel triple combination (26%) [43].

These findings suggest that it would be too early to omit chemotherapy in HER2+ tumors, even though they are HR+ (Table 1). Otherwise, investigators of the TBCRC 006 trial reported that the minimal residual disease after NAT is more common in HR+ (33%) than in HR– tumors (4%). Overall, 54% of patients achieved a good response in this trial. Knowing that pCR is only a prognostic factor in HR- tumors, chemo-free protocol may be an option for HR+ patients despite the low rate of pCR.

In the WSG-ADAPT trial, 380 patients with HER2+ and HR+ tumors were randomized in order to receive trastuzumab-emtansine (TDM1) monotherapy, TDM1 with ET, or trastuzumab with ET, which resulted in pCR rates of 40.5%, 45.8% and 6.7%, respectively. The pCR rate was significantly higher with TDM1, than with the trastuzumab containing chemo-free arm. Addition of ET to TDM1 had no significant effect [53].

The KRISTINE trial also confirmed that the more intensive chemotherapy was associated with improved efficacy. In this study, 444 patients were enrolled and randomized to receive six cycles of TDM1 and pertuzumab, or six cycles of docetaxel,

Table 1. Pathological complete remission rates in neoadjuvant trials with anti-HER2 blockade on HR-positive breast cancers

Type of neoadjuvant therapy	Therapy	Trial	pCR (%)*	pCR rates in pre-/post-menopausal patients (%)
Chemotherapy+trastuzumab	T-DM1	ADAPT (n=119) [53]	41	37.9/44.1
	Trastuzumab+docetaxel	CALGB40601 (n=70) [45]	41	
	NeoSphere (n=50) [43]	20	
Chemotherapy+dual HER2 blockade	T-DM1+pertuzumab	KRISTINE (n=138) [54]	35	
	Trastuzumab+docetaxel+carboplatin+pertuzumab	KRISTINE (n=128) [54]	44	
	Trastuzumab+docetaxel+lapatinib	CALGB40601 (n=69) [45]	41	
	Trastuzumab+docetaxel+pertuzumab	NeoSphere (n=50) [43]	26	
Chemotherapy+dual HER2 blockade+endocrine therapy	Trastuzumab+docetaxel+carboplatin+pertuzumab+ aromatase inhibitor	NSABP B-52 (n=157) [49]	46	
Chemotherapy+trastuzumab+endocrine therapy	T-DM1+endocrine therapy	ADAPT (n=127) [53]	41.5	38.1/45
Trastuzumab+endocrine therapy	Trastuzumab+endocrine therapy	ADAPT (n=129) [53]	15.1	13.6/16.7
Dual HER2 blockade	Trastuzumab+pertuzumab	NeoSphere (n=51) [43]	6	

HER=human epidermal growth factor receptor 2; HR=hormonal receptor; pCR=pathological complete response; T-DM1=trastuzumab emtansine.
*pCR rate for HER2 positive and estrogen receptor positive tumours (pCR rate in %).

CBP, trastuzumab, and pertuzumab; pCR rates of 44.4% and 55.7% have been achieved, respectively. The difference was apparent in HR+ subgroup (37.9% vs. 44.8%), but it was more pronounced between HR− subgroups (53.8% vs. 72.4%) [54]. It is expected that the randomized HELEX study (extension of TBCRC006) will provide additional data regarding the chemo-free treatment of HER2+ tumors (NCT00999804).

The effect of PIK3CA mutation on the success of the therapy was investigated in several trials (GEPARQUINTO, GEPARSIXTO [27], NeoALTTO, and CherLOB [55]). All analyses have found lower pCR rates in patients with PIK3CA mutation receiving anti-HER2 containing regimens. Similar findings have been reported irrespectively of the administered anti-HER2 agent or HR status [9,56-58]. In a subgroup analysis performed on the dataset of the NeoALTTO trial, PIK3CA mutational status, hormone status, and therapeutic approach (single or dual HER2-blockade) were identified as independent predictive factors of pCR. This finding would imply that anti-HER2 therapy is reasonable in PIK3CA mutant tumors, as well. In addition, the possibility of targeting the PI3K-mTOR pathway has also emerged [56].

Additional chemotherapeutic agents

The efficacy of platinum derivatives, such as cisplatin or CBP, in the treatment of breast cancer has been demonstrated by clinical trials. In the phase II GEPARSIXTO study, 588 patients with TN and HER2+ patients were recruited and randomized to receive weekly paclitaxel and liposomal doxorubicin with or without CBP. The benefit of addition of CBP was apparent only in a subgroup of patients presenting TN tumors, as reflected from significantly improved pCR

rates (53.2% and 36.9% for CBP-supplemented and CBP-free therapies, respectively) [27].

This finding was endorsed by the phase II CALGB 40603 trial, which enrolled patients with TNBC. Subjects were randomized according to a 2×2 factorial design to receive neoadjuvant paclitaxel±CBP±bevacizumab, followed by dose-dense doxorubicin plus cyclophosphamide±bevacizumab. Analysis of the results has shown that only CBP improved significantly the pCR rate, from 41% to 54%. The bevacizumab-containing arms had a combined pCR rate of 59% compared with 48% in the bevacizumab-free arms. The arm that included both CBP and bevacizumab had the highest pCR rate (67%) [59].

In the GEPARSIXTO trial, the role of lymphocyte infiltration has also been investigated. The pCR rates among patients receiving CBP were significantly higher in case of tumors showing lymphocyte predominance. Similarly, subgroup analyses of TN and HER2+ patients also indicated the positive association of pCR rates and the presence of lymphocyte infiltration. On the other hand, the effects of inclusion of CBP on DFS were inconsistent, as reported by these trials. According to the GEPARSIXTO trial, patients with TN tumors showed significantly higher DFS as a result of CBP-supplemented therapy. The CALGB 40603 trial, however, reported no evidence on the improvement of DFS.

In the open-label, single-arm trial of Sharma et al. [60], a number of 76 TNBC patients were treated with four to six cycles of docetaxel and CBP, and results demonstrated in a remarkably high pCR rate of 66% (55). Although previous neoadjuvant trials reported that *BRCA* mutant tumors were highly sensitive to platinum agents [61], the GEPARSIXTO trial

found no evidence indicating that the presence of *BRCA* mutation would result in higher efficacy of CBP therapy. These results provide a basis for the incorporation of CBP in the NAT of patients with TNBCs; in the absence of additional data on survival, the routine use of platinum is not recommended, though. Nevertheless, addition of platinum can be justified on an individual basis, if certain risk factors are present, including high-risk, germ-line *BRCA* mutation, and lymphocyte predominance.

In the GEPARQUATTRO study, the effect of addition of capecitabine to anthracycline- and taxane-based NAT was investigated. A total number of 1,509 patients (out of which 445 patients were HER2+) were randomized after four cycles of epirubicin-cyclophosphamide, in order to receive an additional four cycles of docetaxel or four cycles docetaxel-capecitabine combination, or four cycles of docetaxel followed by four cycles of capecitabine. Neither the addition of capecitabine, nor the prolongation of therapy improved the efficacy outcomes as reflected from the similar pCR rates (22.3%, 19.5%, and 22.3%, respectively) [38]. Similarly, according to the findings of the NSABP B-40 trial, the addition of capecitabine or gemcitabine did not improve significantly pCR rate or survival [62]. It should be noted that both trials applied lower docetaxel doses when used in combination with capecitabine. Contrastingly, in the ABCSG-24 phase III trial, Steger et al. [63] randomized 536 patients to receive similar doses of epirubicin-docetaxel combination with or without capecitabine. The pCR rate in the capecitabine-supplemented arm was 23%, which was significantly higher compared to results obtained in the control group (15.4%). This result is consistent with findings of the adjuvant CBCSG-10 study. This trial was designed to investigate the effect of add-on capecitabine therapy in patients sequentially receiving docetaxel and epirubicin. Even though the study did not meet its primary endpoint (i.e., DFS), the relapse-free, disease-free, and the OS were found to be higher in the capecitabine arm [64]. The therapeutic role of capecitabine in the perioperative setting was further endorsed by the CREATE-X study previously mentioned [40]. These results suggest that capecitabine provides therapeutic benefit only when other NAT agents are administered in conventional doses.

Targeted agents other than anti-HER2 or endocrine medication

The benefit of add-on bevacizumab in a NAT setting was investigated by 3 phase III and 2 phase II randomized trials, so far (Table 2). In the GEPARQUINTO trial, which included four cycles of epirubicin-cyclophosphamide and docetaxel with or without bevacizumab, [36] inclusion of bevacizumab in the therapy resulted in significantly higher pCR in patients

with TNBC, whereas no significant effect was observed in patients with HR+ tumor. However, the addition of bevacizumab did not demonstrate any significant effect on the survival rates (DFS or OS) of the HER2− and TN subgroups.

The NSABP B-40 trial aimed to investigate the efficacy of add-on bevacizumab, capecitabine, and gemcitabine by using a 3×2 factorial design. In contrast to the findings of the GEPARQUINTO trial, in this study, the bevacizumab related improvement of pCR was apparent only in patients with HR+ tumors. After a median 4.7-year follow-up, bevacizumab treatment was associated with higher OS (hazard ratio, 0.65; $p = 0.004$) while DFS was not significantly affected [62].

The investigators of the ARTemis trial reported significantly higher pCR rate only in the subgroup of 241 patients with TNBC [65]. With respect to pCR in bevacizumab treated TNBC patients, the phase II CALGB 40603 study found no significant differences, while the SWOG S0800 study reported significantly higher pCR rates in the add-on bevacizumab group [59,66]. In a recent meta-analysis of five randomized trials Nahleh et al. [67] found that bevacizumab significantly increases the pCR rate, both in TN and HR+ subgroups of patients. The inclusion of bevacizumab into NAT regimens requires further investigation, as well as analysis of pooled survival and safety data.

The antidiabetic agent metformin also seems to have therapeutic value in the neoadjuvant treatment of breast cancer. In a small randomized, double-blind trial conducted by Arce-Salinas et al. [68], patients with HR+/HER2− tumors were treated either with metformin or with placebo, in addition to the conventional NAT regimen. Metformin treatment resulted in a higher pCR rate.

According to the result of a phase II trial on patients with TNBC, the addition of CBP and PARP-inhibitor veliparib to NAT led to a remarkably higher pCR rate (26% vs. 52%) [69].

The therapeutic value of add-on veliparib is under investigation in an ongoing phase III trial (NCT02032277). Similarly, rucaparib used in extended adjuvant therapy after NAT has also been subjected to an ongoing clinical investigation (NCT01074970).

IMMUNOTHERAPEUTIC OPTIONS

Since the recognition that the immune system has the greatest potential for the specific destruction of tumors with no toxicity, immune-oncology has become a rapidly growing field of research. The predictive and prognostic role of TIL pointed out the importance of the immune reaction in the pathogenesis of breast cancer [70]. Among solid tumors, breast cancer has moderate immunogenic properties [71], but

Table 2. Efficacy data in neoadjuvant trials investigating bevacizumab

Study	Clinical phase	No. of cases	Standard neoadjuvant regimen	pCR definition	Treatment arms	pCR (breast and axilla) (%)			DFS	OS	Subgroups with prominent therapeutic effect
						All	HR+	HR−			
GeparQuinto [48]	Phase III	1,948	4 Cycles of epirubicin-cyclophosphamide followed by 4 cycles of docetaxel (early nonresponders excluded)	ypT0 N0	8 Cycles of bevacizumab concomitantly with standard NAT	18.4*	7.7	39.3*	At 3 yr: 80.8%	At 3 yr: 90.7%	TN, cT1-3, non-lobular, grade 3
					Standard NAT	14.9*	7.8	27.9*	At 3 yr: 81.5%	At 3 yr: 88.7%	
NSABP B-40 [62]	Phase III	1,186	4 Cycles of docetaxel (+/– capecitabine or gemcitabine) followed by 4 cycles doxorubicin and cyclophosphamide	ypT0 N0	6 Cycles bevacizumab concomitantly with standard NAT 10 Cycles of bevacizumab postoperatively	27.6	16.8*	NR	At 4.7 yr: hazard ratio: 0.8 (p=0.06)	At 4.7 yr: hazard ratio: 0.65* (p=0.004)	HR+, grade 3, node negatives
					Standard NAT	23	11.1*	NR			
ARTemis [65]	Phase III	781	3 Cycles of docetaxel followed by 3 cycles of 5-FU+epirubicin+cyclophosphamide	ypT0/Tis N0	4 Cycles of bevacizumab concomitantly with standard NAT	22*	6	45*	NR	NR	TN, grade 3
					Standard NAT	17*	7	31*			
CALGB 40601 [45]	Phase II	443	12 Cycles of paclitaxel followed by 4 cycles of dose-dense doxorubicin-cyclophosphamide (+/– 4 cycles of carboplatin)	ypT0 N0	9 Cycles of bevacizumab concomitantly with standard NAT	52	-	-	NR	NR	-
					Standard NAT	44	-	-			
SWOG S0800 [66]	Phase II	215	12 Cycles of nab-paclitaxel followed by 6 cycles of doxorubicin-cyclophosphamide	ypT0/Tis N0	6 Cycles of bevacizumab concomitantly with standard NAT	36*	24.2	59.4*	Hazard ratio: 0.89 (p=0.71)	Hazard ratio: 0.84 (p=0.64)	TN
					Standard NAT	21*	18	28.6*			

pCR=pathological complete response; HR+=hormone receptor positive; HR−=hormone receptor negative; DFS=disease-free survival; OS=overall survival; NAT=neoadjuvant therapy; TN=triple-negative; NR=no result; FU=follow-up.
*Significant results.

the higher mutational rate observed in HER2+ and TN tumors makes these subtypes promising targets for different immuno-therapies.

The higher level of genetic instability and consequently, the higher frequency of mutations produce new antigens, which eventually lead to increased immunogenicity. A number of trials are investigating the role of programmed death protein 1 and programmed death-ligand 1 inhibitors (pembrolizumab [72] or atezolizumab [73]) in breast cancer; so far, promising results have been only observed in metastatic breast cancer. In addition, antitumor activity in metastatic breast cancer has been confirmed using autologous dendritic cell vaccine [74] or an antibody-chemotherapy (irinotecan) complex [75], even though no data are available regarding its use in neoadjuvant setting.

ENDOCRINE THERAPY

About 2/3 of breast cancers are HR+, which makes the use of endocrine agents in the neoadjuvant setting reasonable. ET alone results in pCR rates less than 10% [76]. However, tumors with high HR expression and low presence of proliferative markers, such as HER2−, are also associated with low pCR rates in standard chemotherapeutic setting. In luminal A-like diseases, neoadjuvant ET is a recommended therapeutic option [77], since it leads to a therapeutic response similar to that of standard chemotherapy, as observed after a retrospective a retrospective analysis using 21-gene recurrence scores [78]. Two trials have also compared the efficacy of chemotherapy and ET, and found that the main endpoints, such as OS rate, pCR, and the rate of breast conserving surgery, showed no significant difference [79,80]. Furthermore, a recent meta-analysis pooling the data of 3,490 patients, has indicated that clinical and radiological response rates, as well as breast conserving surgery rates obtained for neoadjuvant chemotherapy and ET are similar [81]. Although studies did not identify patient subgroup(s) for which neoadjuvant ET could be more advantageous than standard chemotherapy, the higher toxicity of the latter should be considered during therapy planning.

During treatment, change in Ki-67 value can be a surrogate marker for the efficacy of neoadjuvant ET. The preoperative endocrine prognostic index (PEPI score) can also serve as a basis for selection of patients who could benefit from ET alone [76]. The aromatase inhibitors (AI) were found to be more effective than tamoxifen. Furthermore, longer preoperative treatment with AIs led to higher pCR rate. Approximately one-third of the patients benefited from extended ET (i.e., 6–12 months), while the probability of progression remained

low (0.8%–12%). Therefore, 4 to 8 months of AI therapy is recommended over tamoxifen in postmenopausal breast cancer patients and in selected premenopausal patients who are already receiving LHRH-agonist [13,77]. There are several ongoing trials investigating the combination of ET and other targeted therapies. Using this approach the parallel blockade of intracellular pathways and the reversal of endocrine resistance could be achieved. The PI3K/mTOR pathway, CDK4/6, HDAC, and immune checkpoints are the most promising and widely investigated targets [82].

The results of a phase II trial showed that everolimus improved antiproliferative response, but this therapy was associated with more side effects and no survival data have been published, so far [83]. In a phase II trial, HER2− patients received lapatinib in addition to letrozol, if wild-type of *PI3K* gene was present. This therapeutic strategy eventually led to an increased rate of pCR [84]. Another study with similar design failed to prove the benefit of add-on gefitinib in anastrozole therapy [85].

Currently, the following agents are under clinical investigation: the CDK4/6 inhibitor ribociclib (NCT02712723) and palbociclib (NCT02296801, NCT02530424), palbociclib and olaparib in a personalized therapy (NCT02624973), the RET inhibitor lenvatinib (NCT02562118), the PI3K inhibitor buparlisib (NCT01923168) and taselisib (NCT02273973).

CONCLUSION

In the last decades, NAT of breast cancer has gained a considerable therapeutic importance. NAT offers several advantages in comparison to standard adjuvant therapies. Provided that NAT is commenced during the early phase of the therapy, it may allow the possibility to evaluate treatment efficacy and avoid ineffective, futile therapy, potentially resulting in improved survival rates, at least in certain subgroups of breast cancer. According to our current knowledge, NAT is recommended primarily for resectable TN and HER2+ tumors, and consists of anthracycline and taxane components, as well as an anti-HER2 agent in presence of HER2 positivity. Although in endocrine sensitive tumors, NAT rarely results in pCR, it may still provide therapeutic benefit. However, in order to determine the role of NAT in early breast cancer treatment, long-term follow-up data provided by clinical trials are required. It has not yet been clarified whether more intensified or long-term administration of NAT regimes, or addition of other chemotherapeutic or targeted agents would be beneficial, at least for some well-defined subgroups of patients; such conceptions are promising and have been subjected to ongoing clinical investigations. Nevertheless, the therapeutic po-

tential of NAT is expected to be further improved on the basis of biomarker analysis, eventually leading to personalized cancer therapy.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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