Primary/Neoadjuvant Treatments

16

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Abbreviations

(w)Pac	(Weekly) paclitaxel
[HR]	Hazard ratio
[OR]	Odds ratio
AC	Doxorubicin, cyclophosphamide
adjChT	Adjuvant chemotherapy
adjRT	Adjuvant RT
AEs	Adverse events
AI	Aromatase inhibitor
AJCC-UICC	The American Joint Committee on Cancer and the International Union for Cancer Control
ALND	Axillary lymph node dissection
A-Ta-ChT	Anthracycline- and taxane-based chemotherapy
BCS	Breast-conserving surgery
Cb	Carboplatin
CHF	Congestive heart failure
CMF	Cyclophosphamide, methotrexate, fluorouracil
CNB	Core needle biopsy
CR	Complete response
c-stage-	Clinical stage-
CT	Computerized tomography
ddAC	Dose-dense AC
DFS	Disease-free survival
DiR	Distant recurrence
eBC	Early-stage breast cancer
EC	Epirubicin + cyclophosphamide
EFS	Event-free survival
ER(−)	Estrogen receptor-negative
ER(+)	Estrogen receptor-positive
FEC	Fluorouracil + epirubicin + cyclophosphamide
feN	Febrile neutropenia
FNAB	Fine needle aspiration biopsy
FNR	False-negative rate
FPR	False-positive rate
G-CSF	Granulocyte colony-stimulating factor
HER2	Human endothelial growth factor receptor 2
HER2(−)	HER2 negative
HER2(+)	HER2 positive
HP	Trastuzumab + pertuzumab
HR(−)	Hormone receptor-negative
HR(+)	Hormone receptor-positive
LABC	Locally advanced breast cancer
LHRH	Luteinizing hormone-releasing hormone
LN	Lymph node
LoR	Local recurrence
LVEF	Left ventricular ejection fraction
mAB	Monoclonal antibody
MMG	Mammography
MRI	Magnetic resonance imaging

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nab-P	Nanoparticle albumin-bound paclitaxel
NACT	Neoadjuvant chemotherapy
NAET	Neoadjuvant endocrine therapy
NPV	Negative predictive value
NX	Vinorelbine + capecitabine
ORR	Overall response rate
OS	Overall survival
PARP	*Poly-ADP-ribose polymerase*
PARPi	Poly-ADP-ribose polymerase inhibitor
pCR	Pathologic complete response
PD	Progressive disease
PE	Physical examination
PEPI	Preoperative endocrine prognostic index
PIK3CA	Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha
PR(−)	Progesterone receptor-negative
PR(+)	Progesterone receptor-positive
PS	Performance status
RCT	Randomized clinical trial
RFS	Recurrence-free survival
RT	Radiotherapy
SLNB	Sentinel lymph node biopsy
T	Docetaxel
TC	Docetaxel + cyclophosphamide
TCb	Docetaxel + carboplatin
T-DM1	Ado-trastuzumab emtansine
TH	Docetaxel + trastuzumab
THP	Docetaxel + trastuzumab + pertuzumab
TILs	Tumor-infiltrating lymphocytes
TK	Tyrosine kinase
TKi	Tyrosine kinase inhibitors
TN	Triple negative
TNBC	Triple-negative breast cancer
TNM	Tumor, node, metastasis
TP	Docetaxel + pertuzumab

16.1 Introduction

Neoadjuvant therapy is defined as the systemic treatments administered prior to definitive surgery in BC. Although NAET and immunotherapy are under investigation in a selected group of patients, primarily, neoadjuvant therapy refers to systemic chemotherapy.

The eighth edition of the AJCC-UICC staging manual, which incorporates contemporary biologic factors into the traditional anatomic TNM (tumor, node, metastasis) classification, is now being used for BC staging [1].

BC is a heterogeneous disease varying widely in histology, grade, proliferative rate, HR/HER2 status, and molecular/genetic features. Genomic analysis of BCs identifies four groups, similar to the intrinsic subtypes defined by gene expression profiling. The St. Gallen International Breast Cancer Conference recognized that BC should not be treated as a single disease and recommended defining disease by molecular subtype using genetic array testing or approximating tumors by ER, PR, HER2, and Ki-67 status [2]. The international consensus now regards grouping tumors into surrogate intrinsic subtypes as the optimal way to stratify patients for prognosis and treatment [3].

16.2 The Principles and Rationale of NACT for Breast Cancer

The prominent objectives of NACT from the clinical vantage point are to eradicate micrometastatic disease, improve OS, decrease the extent of surgery, provide prognostic information, select candidates for additional treatment, and test de-escalation/escalation strategies.

In nonmetastatic invasive BC, neo(adjuvant) systemic treatments are aimed at controlling micrometastatic disease and preventing DiRs. Despite the hypothesis that OS could be improved with NACT since systemic treatment was initiated earlier in patients with a high risk of DiR, RCTs have shown that the long-term outcomes of pre- and postoperative systemic treatment are equivalent [4].

From the surgeon's perspective, the primary goal of NACT is tumor or nodal downstaging to increase tumor resectability and decrease surgical morbidity. Although it evolved for LABC patients, in whom even mastectomy would not

be a treatment option, currently NACT can be applied to patients with operable BC to avoid radical mastectomy. With downstaging, BCS can be performed instead of radical surgery, leading to better cosmesis with breast reconstruction; the extension of ALND can be limited, and postoperative complications can be reduced [5, 6].

Numerous clinical studies compare NACT and adjChT in women with eBC who are surgical candidates. A meta-analysis including 4756 women's individual patient data in 10 randomized trials investigated the long-term benefits and risks of NACT and the influence of tumor characteristics on the outcome [7]. The patients allocated NACT had an increased frequency of BCS (65% with NACT vs. 49% with adjChT). After a median follow-up of 9 years, NACT was associated with more frequent LoR than was adjChT: the 15-year LoR was 21.4% for NACT versus 15.9% for adjChT. No significant difference between NACT and adjChT was noted for DiR (15-year risk, 38.2% for NACT vs. 38.0% for adjChT) and BC mortality (34.4% vs. 33.7%). As shown in another meta-analysis of 14 studies, including 5500 women's data, compared with adjChT, NACT results in as follows [8]:

- Reduced risk of modified radical mastectomy ([HR] 0.71)
- Equivalent OS ([HR] 0.98) and DFS ([HR] 0.97)
- Moderately increased risk of LoR ([HR] 1.21) which is assumed to be the result of higher BCS rates obtained with NACT

Care should be taken to interpret this possibility because some of the trials analyzed used chemotherapy regimens that are no longer standard and did not include targeted therapies, and some used nonstandard locoregional management [4]. Even if so, a small increase in LoR with NACT causes a limited concern as it does not seem to affect DFS or OS.

pCR is defined by the absence of invasive carcinoma in the breast and LNs after NACT. In patients treated with NACT, pCR has prognostic significance. In patients achieving pCR compared to patients with residual invasive disease after NACT, significant improvements were recorded in both DFS ([HR] 0.48) and OS ([HR] 0.48) [9]. This improvement is more pronounced in patients with more aggressive BC subtypes such as HER2(+) and TNBC. The prognostic weight of pCR is lesser among patients with HR(+) and low-grade BC, probably due to tumor biology and the efficacy of adjuvant ET [10]. pCR rate is recognized as a valid surrogate endpoint in the neoadjuvant setting [11].

Another benefit of NACT is that it provides the necessary time for appropriate genetic testing and the planning of breast surgery and reconstruction. Moreover, NACT offers the investigators the opportunity to examine radiological imaging and especially in patients with residual disease, to gather tumor specimens and blood samples, before, during, and after NACT. These collected data will guide the identification of predictive biomarkers specific to the tumor or the patient, regarding response or resistance to therapy. At present, personalization of therapy has not yet been found to be better in cases of poor response to NACT. Nonetheless, NACT creates an opportunity to identify candidate patients for clinical trials in which novel agents may be used in an adjuvant setting in patients with residual disease after standard preoperative systemic treatment [12].

16.2.1 Candidate Patients for NACT

The potential indications of NACT are summarized under four main headings:

16.2.1.1 Locally Advanced Breast Cancer

LABC patients, defined as stage III disease with T3 (>5 cm), T4 (tumor invading the chest wall +/skin) lesions, or N2–N3 nodal involvement, are ideal NACT candidates, regardless of the subtype, because these patients are not suitable for primary surgery or mastectomy is required due to tumor size and extent. Systemic therapy is warranted because of the risk of DiR [3].

16.2.1.2 Selected Patients with Early-Stage Breast Cancer

If BCS is not possible due to high tumor-to-breast ratio or if the cosmetic outcome is suboptimal due to tumor localization, patients with stage I–II eBC are also eligible candidates for NACT. Also, NACT may be recommended for patients with HER2(+) or TNBC, with even smaller tumors (T1c), who are expected to receive chemotherapy at some point in the course of treatment; and these subtypes are associated with a high probability of pCR. The patients with intermediate high-risk (≥T2 and/or N+) HER2(+) or TNBC must receive NACT, as this strategy not only increases the chance of less aggressive surgery but identifies patients who would need further adjuvant therapy if residual disease remains after NACT [13].

The role of NACT in patients with luminal-type eBC is less pronounced. In HR(+)HER2(−) tumors, chemotherapy may rarely provide a pCR. However, NACT can often lead to tumor shrinkage that may be sufficient to provide BCS in a patient requiring a mastectomy. Whether NACT or NAET should be recommended for such patients is the subject of debate and depends on many other factors, such as the age and concomitant diseases of the patient and the c-stage of the disease [14].

16.2.1.3 Limited Node-Positive Disease

The downstaging of ALNs in patients of eBC with limited N+ (cN1) disease is another indication for NACT, regardless of the size of the primary tumor. ALND has been the conventional standard surgical approach in N+ patients, whether or not the patient received NACT, whereas ALND, as compared to SLNB, is associated with more lymphedema, motion restriction, postoperative pain syndromes, and other locoregional complications [15]. NACT leads the conversion of cN+ to pN0, especially in patients with more aggressive BC subtypes. According to the results of the ACOSOG Z1071 (Alliance) trial, the likelihood of nodal conversion is lower in HR(+)HER2(−) disease (21.1%) than that in women with HER2(+) and TNBC (64.7%, 49.4%, respectively) [16]. Also, the overall residual burden in the ALNs is higher in HR(+)HER2(−) disease, after NACT. The results of current clinical studies indicate that most of these patients can be treated effectively with SLNB and RT without lymphedema and other complications.

16.2.1.4 Patients with Temporary Concerns About Surgery

NACT is also a suitable option for patients who have medical contraindications for primary surgery at the time of diagnosis but who are expected to undergo surgery in the future (such as women diagnosed with BC during pregnancy).

16.2.2 Pretreatment Evaluation

16.2.2.1 Evaluation of the Tumor

The histopathological diagnosis should be made according to the WHO classification, and the surrogate intrinsic subtype should be determined according to the current guidelines by testing ER, PR, HER2 status, and Ki-67 proliferation rate before starting treatment, in all patients presenting with a new diagnosis of BC. Image-detectable markers should be inserted into the tumor before starting NACT. The clip witness that the tumor site has been removed, notably when NACT significantly reduces or eradicates the tumor. It also directs the pathological evaluation of the surgical specimen [3, 4].

16.2.2.2 Radiological Imaging

Radiological imaging should be performed for staging of the disease before NACT. In most cases, breast ultrasound is sufficient to document tumor size. However, breast MRI is more sensitive in determining the extent of the disease, especially in patients with dense breast tissue on a mammogram; detecting the presence of multicentric disease; deep axillary and internal mammarian LN metastases; or invasion of the chest wall. On the other side, MRI is being criticized for having a high FPR resulting in overestimating the extent of disease, which in turn increases the frequency of mastectomies [17].

Since the detection of metastatic disease will change the patient's treatment plan, in patients with symptoms and signs that may be related to

occult metastatic disease and in asymptomatic women presenting with c-stage III (large tumors (e.g., ≥5 cm), cN+) or IBC, it is recommended to complete systemic staging with thoracoabdominal CT and bone scintigraphy [3, 4]. FDG-PET-CT scan may supersede traditional imaging for staging high-risk patients [18].

16.2.2.3 Assessment of the Regional Lymph Nodes

PE of the breast and the axilla is essential for all of the patients with a new diagnosis of BC. Since PE is neither a sensitive nor reliable method to ascertain the status of the ALNs, axillary ultrasound is required for those who have no palpable LNs. Ultrasound-guided FNAB/CNB should be performed to confirm pathological involvement in patients with suspicious LNs.

The diagnostic yield of FNAB relies on the skills and the experience of the radiologist and cytopathologist. Therefore, the sensitivity (40–91%) and specificity (90–100%) of axillary FNAB/CNB vary widely across many studies. Although FNR have been reported in a range of 6–11%, the detection of a positive LN in a cN0 patient directs the surgical approach to the axilla after NACT [19].

If FNAB/CNB confirms an axillary nodal involvement, insertion of a radiopaque clip into this particular node is recommended to identify the target in case of its disappearance after NACT. The evidence supports that resection of the clipped node along with SLNB, called as *targeted axillary dissection*, significantly reduces FNR from 10.1 to 1.4% following NACT [20].

For those with cN0, SLNB may be recommended before or after NACT, but the procedure seems less accurate after NACT [21].

16.2.3 Treatment Options

16.2.3.1 Neoadjuvant Chemotherapy

Chemotherapy Options

All modalities and regimens used in the adjuvant setting may also have a place in the neoadjuvant setting. The most frequently used regimens contain anthracyclines proceeded by taxanes. Anthracycline-based treatments are preferred in "high-risk" patients with large tumor size, N+, and HER2(−)BC. Nonetheless, anthracycline-free therapies serve a reasonable option to avoid potential cardiac toxicities and secondary MDS/AML.

Anthracycline-Based Regimens

One of the main goals of NACT is to ensure that patients receive effective adjChT. Therefore, most women receiving NACT should have standard treatment with four cycles of dose-dense anthracycline-based chemotherapy (AC or EC) followed by paclitaxel administered either every 2 weeks for four cycles or weekly for 12 cycles (e.g., 4ddAC/4Pac; 4ddAC/12wPac). Docetaxel, which is given every 3 weeks, is an acceptable option instead of paclitaxel [4].

The rationale for the use of A-Ta-ChT preoperatively comes directly from clinical trials of neoadjuvant treatment. The addition of a taxane to an anthracycline-based regimen, either concurrently or sequentially, is associated with increased response rates. The Oxford meta-analysis of adjChT studies showed that 4 AC was equally efficient as 6CMF [22].

Recently published another meta-analysis determined that adjuvant dose-dense (every 2 weeks) anthracycline-based treatment improved the outcomes compared to the standard (every 3 weeks) scheme [23].

Non-anthracycline-Based Regimens

Anthracycline-free treatment options may be preferred in NACT as well as adjChT in some fragile, elderly patients who have significant comorbidities such as cardiac disease, uncontrolled diabetes, and hypertension or who wish to avoid uncommon but severe side effects of the anthracyclines such as secondary leukemia and cardiac toxicity. Since TC is a frequently used regimen in HER2(−) patients for this purpose in the adjuvant setting, it is acceptable for NACT. There are few studies on neoadjuvant administration of TC. Data on the efficacy of TC suggest lower pCR rates in the HR(+)HER2(−) patient group (7% vs. 17%), but it is known that

this group of patients is less likely to achieve pCR [24].

Although TC is a reasonable treatment option for TN patients with contraindications for anthracycline use, based on the evidence that adding platinum to NACT provides additional benefits in TNBC, carboplatin combination with docetaxel, paclitaxel, or gemcitabine may also be considered as an alternative to TC.

Choice of Taxane

The standard NACT employs either T(/3wks) alternatively, wPac, considering their efficacy and tolerability. However, nab-paclitaxel provides another favorable option in patients with a hypersensitivity reaction to taxanes or contraindications to steroids, typically administered with T/Pac, such as uncontrolled diabetes or steroid psychosis [25, 26]. Although the preliminary results of these studies are encouraging, it is not recommended to use nab-paclitaxel except for patients with contraindications for standard taxanes, while long-term results are being expected.

Treatment Schedule and Sequence

NACT is usually administered using standard adjChT agents, doses, and schedules. There is no proof supporting that distinct regimens should be used in NACT other than adjuvant therapy options except for carboplatin addition to NACT in TNBC.

Preliminary evidence from a retrospective analysis of more than 1400 eBC patients receiving both A/Ta in NACT suggests that Ta → A sequence was associated with a higher likelihood of pCR and lower risk of relapse compared to A → Ta [27]. The only prospective neoadjuvant trial to investigate whether the sequence of A/Ta affects pCR was the Neo-tAnGo study [28]. In this phase III, open-label trial 831 patients were randomized in a 2×2 factorial design, and 4EC → 4Pac (±gemcitabine) was compared with the vice versa sequence. The pCR rate in patients receiving paclitaxel first was 20% vs. 15% in the group receiving EC first. The difference was statistically significant.

While these data support the taxane implementation first, they are not persuasive enough to accept this as the preferred approach. A recent meta-analysis also assessed whether the sequence in which A/Ta is administered affects outcomes for patients with eBC receiving (neo)adjuvant therapy [29]. The authors discussed the included trials' pitfalls and concluded that currently available data do not support a change in the standard practice of delivering A → Ta.

16.2.3.2 NAET in HR(+) Disease

Although ET is the mainstay of adjuvant treatment for HR(+)BC, its role in the neoadjuvant setting is controversial. There are limited data comparing NACT to NAET, and the best available evidence comes from phase II trials. Some patients with HR(+)BC may benefit from NAET. Tumor grade, ER/PR expression intensity, and Ki-67 can help to determine the likelihood of response to chemotherapy [30]. Recent data from multiple small studies are still immature but suggest that gene expression assays such as OncotypeDx, PAM50, or 70-gene profile may also help oncologists to choose between treatment options. Data from retrospective analyses show that PEPI score may identify low-risk groups with no meaningful benefit from additional chemotherapy [31].

Three different occasions have been discriminated for NAET. (1) Patients too frail for surgery are candidates for NAET in order to control the disease. (2) Patients with inoperable tumors or not suitable for BCS, who have relative contraindications to chemotherapy are candidates for NAET in order to achieve downstaging. (3) Patients, in whom the indication for chemotherapy is uncertain due to intermediate risk, may undergo NAET in order to perform in vivo sensitivity testing.

The use of AIs (exemestane, letrozole, or anastrozole) instead of tamoxifen in NAET was associated with a higher ORR (55% vs. 36%; [OR] 1.49) and a higher BCS (45% vs. 35%; [OR] 1.62) in postmenopausal women. Treatment with any of the AIs resulted in similar clinical response rates [30]. The incidence of pCR was low (<10%); thus, it could not be considered as a valid surrogate of clinical outcome [32]. The rates of BCS were not statistically different.

Therefore, for postmenopausal women, administration of AI is preferred [14].

In contrast to postmenopausal women, NAET data comes from small phase II studies, in premenopausal women. The limited data on hand suggests that the results are worse than chemotherapy. LHRH-agonist +AI combinations are considered to be superior to tamoxifen. NAET in premenopausal patients should be considered experimental until this issue is evaluated in RCTs [33].

A response to NAET may not be evident for 3–4 months, and maximal response may not be achieved until much later. Treatment duration should be at least 3–6 months according to current data.

Several ongoing phase II trials are searching for the answer if dual combination therapies could improve the efficacy of NAET by combining ET with CDK4/6 inhibitors such as palbociclib, ribociclib, abemaciclib, or PI3K inhibitors such as taselisib and copanlisib [14]. The efficacy and safety results of phase III clinical trials with these agents in the neoadjuvant setting should be waited before including these agents as a treatment option in the eBC.

16.2.3.3 Neoadjuvant Treatment in HER2(+) Disease

HER2 gene amplification and receptor overexpression leading to constant activation of downstream signaling pathways cause a biologically more aggressive malignancy but also increase susceptibility to cytotoxic chemotherapy. Fortunately, the addition of HER2-targeted agents to chemotherapy creates a synergistic effect and further increases the chemosensitivity, and compared to other BC subtypes, a higher percentage of HER2(+) patients is achieved to pCR. Both cCR and pCR rates were higher (>60%) with HER2-targeted therapies, reflecting better DFS and OS rates in HER2(+)BC patients [34].

In HER2(+)eBC, the standard neoadjuvant treatment consists of HER2-targeted therapy (trastuzumab w/wo pertuzumab) in combination with chemotherapy. According to international guidelines, taxane-containing chemotherapy should be combined with dual blockade of HP, followed by breast surgery, radiotherapy (if indicated), completion of 12 months of HER2-directed therapy, adjuvant ET (depending on the tumor biology), and ultimately follow-up. Based on achieving pCR or not after NACT, adjuvant therapy may be adjusted.

Components of Therapy

Biologic Therapy

HER2-Targeted Therapy in Adjuvant vs. Neoadjuvant Setting

Significant benefits in DFS, OS, LoR, and DiR were seen in four RCTs (HERA, NCCTG N9831/NSABP B-31, BCIRG 006) and two meta-analyses for the addition of trastuzumab to adjChT. They showed statistically significant improvements in DFS in favor of trastuzumab with [HR] 0.48–0.67 and OS with [HR] 0.59–0.67, with an absolute difference in OS of 1–2.5%. In the combined analysis, a 10-year DFS of 73.7% was reported with a relative risk reduction of 37% for OS. The risks for CHF and LVEF decline were increased with trastuzumab, but fortunately reversible if monitored carefully and immediately stopped if indicated. Cardiac events occur in 1.9–3.8% in combination of anthracycline and trastuzumab treatment [35]. On this basis, trastuzumab became the standard of care in the adjuvant treatment for HER2(+)BC patients.

In 2008, the Early Breast Cancer Trialists Collaborative Group showed the same long-term outcome for standard chemotherapy if applied either in the pre- or in the postoperative setting and additional benefit in HER2(+)BC in the neoadjuvant setting [36].

Trastuzumab

Trastuzumab is a humanized mAB, consisting of two antigen-specific sites that bind to the extracellular domain of the HER2, and prevents the activation of its intracellular TK. The role of trastuzumab in HER2(+)BC in improving pCR rates, EFS, and OS was demonstrated clearly and strongly in the neoadjuvant setting as well as the adjuvant setting [37].

In the phase II NOAH trial, the neoadjuvant A-Ta-ChT was given w/wo trastuzumab (neoadjuvantly in combination with chemotherapy fol-

lowed by adjuvant monotherapy to complete a year of therapy) in patients with LABC. 38% of HER2(+) patients in the trastuzumab arm achieved a pCR vs. only 19% in the control arm. The 3-year DFS was 71% and OS 87% with trastuzumab compared with 56% and 79%, respectively, with chemotherapy alone. With long-term (5.4 years) follow-up, the survival benefit in the trastuzumab group was maintained, suggesting the superiority of the NACT+trastuzumab combination at eradicating micrometastases even among patients with an excellent locoregional response. Patients who achieved a pCR under treatment with trastuzumab had a significantly improved DFS ([HR] 0.29) and OS ([HR] 0.27), again demonstrating that pCR is associated with a better prognosis in HER2(+)BC patients receiving HER2-targeted therapy [38].

The TECHNO trial was also one of the first trials to analyze the pCR rate with NACT + trastuzumab and its effect on prognosis. A total of 39% of patients achieved pCR, proving the high efficacy of NACT + trastuzumab. The 3-year OS was 96.3% in those with a pCR compared with 85.0% in those without pCR. pCR was the only significant prognostic factor for patient survival (DFS [HR] 2.49; OS [HR] 4.91) [39].

In a 2012 meta-analysis, among almost 2000 patients with HER2(+) disease, the addition of trastuzumab to NACT increased the pCR rate from 23 to 40%. pCR was associated with better long-term outcome among patients with HER2(+) BC, irrespective of HR status (EFS [HR] 0.39; OS [HR] 0.34) [40].

Pertuzumab

Pertuzumab is a recombinant mAB that binds to a different epitope (subdomain II) on HER2 than trastuzumab, blocking the ligand-dependent hetero-dimerization of HER2 with other HER family members, including EGFR, HER3, and HER4, which is believed to be a substantial mechanism of resistance to trastuzumab. HP has a synergistic action; indeed, the combination is more effective than with either antibody alone [41]. The addition of pertuzumab to NACT+trastuzumab is indicated for patients with HER2(+) inflammatory, LABC, or eBC (either tumor ≥2 cm in diameter or N+, at a high risk of recurrence) [42].

The first neoadjuvant study investigating pertuzumab was NeoSphere, followed by the TRYPHAENA trial. A dual HER2-blockade using HP combined with chemotherapy achieved pCR rates in the range of 50–60% [43, 44].

In the 4-arm, phase II NeoSphere trial, patients received NACT with either TH, TP, THP, or HP without chemotherapy. All patients received adjuvant FEC. The highest pCR rate was observed in the THP arm (45.8%). In contrast, TH was associated with a pCR of 29.0%, TP with a pCR of 24.0%, and HP with a pCR of only 16.8%. The 5-year PFS and DFS in patients who received THP were 86% and 84%, respectively. While the 5-year PFS does not demonstrate a benefit associated with THP ([HR] 0.69; 95% CI, 0.34–1.40), the study was not powered to detect differences in this endpoint. Women across all groups who achieved pCR benefitted from a longer PFS than those without pCR (85% vs. 76%; [HR] 0.54; 95% CI, 0.29–1.00) [43].

The TRYPHAENA was a phase II cardiac safety study that randomized 225 treatment-naive women with operable, locally advanced, or inflammatory HER2(+)BC to receive one of three neoadjuvant treatments: FECHP+THP, FEC + THP, and TCHP. Following surgery, all patients received trastuzumab to complete 1 year of therapy. The primary endpoint of the study was cardiac safety related to the timing of administration of HP relative to an anthracycline-based chemotherapy regimen. The study was not powered to compare pCR rates and long-term outcomes between the treatment arms and did not include a non-pertuzumab-containing arm. pCR rates were consistently high (approximately 60%) and similar across all treatment groups. Long-term DFS and PFS were similar between groups. Patients who achieved pCR had improved DFS [44]. Similar incidences of grade > 3 AEs were observed. In the absence of prophylactic G-CSF, the incidence of feN was 9.3–18.1%. Rates of cardiotoxicity were comparable between the two groups receiving anthracycline-based treatment and slightly lower in the TCHP arm.

The GeparSepto study reported a similar pCR rate of 58% among 400 patients with stage II–III HER2(+)BC treated with neoadjuvant paclitaxel or nab-paclitaxel followed by EC, with concurrent HP [45]. Including all intrinsic subtypes, pCR was 38% for the nab-paclitaxel group vs. 29% in the paclitaxel-treated group. The main additional benefit of nab-paclitaxel on pCR was shown for TNBC [26].

Even though it increases the incidence and severity of treatment-related diarrhea as well as the hematologic toxicities, dual blockage with HP is suggested in the neoadjuvant setting, based on the evidence that pertuzumab enhances locoregional responses [36].

For some patients with significant comorbidity or low-risk (c-stage I–IIA) disease, the potential for added toxicity associated with pertuzumab may outweigh the benefit. For such patients, a risk-benefit discussion regarding the use of pertuzumab should be engaged.

Chemotherapy Backbone for HER2(+) Disease

The optimal chemotherapy backbone for dual HER2-blockade in the neoadjuvant setting for eBC is unknown. The following neoadjuvant regimens may be considered standard for HER2(+) BC.

Anthracycline-Based Treatment

Extensive, RCTs (ACOSOG Z1041, NSABP B-41, GeparQuinto) used the historical standard of high-risk HER2(+)BC. These studies show a pCR rate of up to 50% in patients with HER2(+) disease receiving A-Ta-ChT + trastuzumab. In each of these studies, the pCR rate was higher in patients with HR(−) compared to HR(+) [37, 47, 48].

Non-anthracycline-Based Treatment

In the light of the phase II studies and the phase III TRAIN-2 trial, taxane-carboplatin-trastuzumab (±pertuzumab) combinations can be preferable alternatives to anthracycline-based regimens in the neoadjuvant setting in patients with HER2(+)BC, depending upon lesser toxicity and equivalent pCR rates.

The TRAIN-2 study was an open-label, randomized, phase III trial, including 440 patients with stage II–III HER2(+)BC [49]. All patients received HP and were randomly assigned (1:1) to the anthracycline group (3FEC + H followed by 6PacCbHP) or the non-anthracycline group (9PacCbHP). pCR rates did not differ between both arms (67% vs. 68%). Grade 3–4 feN (10% vs. 1%) was more common with anthracyclines, as grade > 2 decline in LVEF (29% vs. 18%).

Alternatives for Those with Low-Risk Disease or Comorbidities

Although it is not the preferred approach, it is possible to translate the less intensive adjuvant regimens into the neoadjuvant setting in a highly selected group of patients. For elderly patients who do not have pre-existing peripheral neuropathy but who are not candidates for A-Ta-ChT due to their limited PS, 12–18wPacH(P) may be preferred. This approach is considered superior to dose-reduced docetaxel-based regimens [46].

For patients with low-intermediate-risk, HER2(+)BC, several non-anthracycline, less intensive chemotherapy options exist, reflecting their efficacy and tolerability in the adjuvant setting. For example, in patients with c-stage I (T1N0) HER2(+)BC in whom NACT is warranted according to the tumor size or location or the need to delay surgery, 12wPacH may be used [50]. Similarly, for patients with c-stage IIA disease with a tumor <3.5 cm, a shorter course of NACT consisting of 4-6TCH(P) may be considered [51].

Timing of HER2-Targeted Therapy

For patients receiving an anthracycline-based regimen as part of NACT, the HER2-targeted therapy is typically administered concurrently with a taxane, either following completion of or before administration of the anthracycline. The timing of HER2-directed agents may be important to decrease the incidence of cardiotoxicity, which is approximately 5% for those who are also being treated with an anthracycline. While ACOSOG Z1041 and TRYPHAENA studies did not demonstrate an increase in cardiac events with concurrent administration of an anthracycline and HER2-targeted therapy, they also did not demonstrate a benefit in terms of pCR rate

[37, 44]. Thus, sequential administration of anthracyclines and HER-directed therapies is recommended. These patients should be monitored closely for cardiotoxicity.

Tumor Prognostic Features in HER2(+)BC

Intrinsic features of the tumor, such as HR status, intrinsic subtype, *PIK3CA* mutation status, and the presence or absence of TILs may explain differences in pCR rates between HER2(+) patients and may also have prognostic significance. However, at present, outside of a clinical trial, altering a HER2(+) patient's planned neoadjuvant regimen based on these features is not recommended [46].

16.2.3.4 Neoadjuvant Treatment in Triple Negative Disease

(Neo)adjuvant chemotherapy is the standard systemic treatment for early TNBC, and A-Ta-ChT regimens constitute the current standard of care. In previous pivotal neoadjuvant studies, patients with TNBC had significantly higher responses to A-Ta-ChT than those with other BC subtypes and achieved approximately 40% pCR. NACT is recommended for TNBC tumors >0.5 cm because of their aggressive behavior, although guidelines generally recommend similar adjChT for each BC subtype [52].

The Role of Platinum-Based Compounds

The addition of Cb to wPac for TNBC (regardless of germline *BRCA1/2* mutation status) is controversial. Although there is evidence of significant improvement in the pCR rate, its effect on DFS is uncertain. The addition of carboplatin increases the AEs, primarily hematological toxicities, requiring dose modifications [53].

Some authors prefer the addition of carboplatin at a high dose (AUC 5–6) every 3 weeks or a low dose (AUC 2) weekly in patients with tumors >3 cm, cN+, or stage III TNBC. However, there is a group of considerable experts who do not add carboplatin to NACT. Although international guidelines do not recommend the routine addition of carboplatin to standard NACT regimens, carboplatin has been added to the control arm in several contemporary RCTs evaluating NACT for TNBC.

The results of the three large neoadjuvant RCTs (CALGB 40603, GBG GeparSixto, and BrighTNess) showed higher pCR rates in TNBC with the addition of carboplatin to A-Ta-ChT [54–56].

The addition of carboplatin was not only associated with an increased pCR rate but also resulted in a significant improvement in GeparSixto with a DFS rate of 85.8% with carboplatin versus 76.1% without carboplatin ([HR] 0.56) and a clinically meaningful albeit statistically not significant improvement in DFS (absolute 5%) in the CALGB 40603 study [54, 55]. Furthermore, the results of the GeparSepto trial suggest particular benefit from using nab-paclitaxel instead of paclitaxel for patients with TNBC, which was not observed in the ETNA trial [25, 57].

In the double-blind BrighTNess study, 634 patients with stage II–III TNBC were randomized to PacCb or PacCb+veliparib (oral PARPi) arms. Carboplatin addition increased the pCR rate from 31 to 58%, while the addition of veliparib to carboplatin did not increase the pCR rate further (53%). The addition of carboplatin has been associated with an impressive increase in the pCR rate, not only for those carrying a deleterious BRCA mutation (50% vs. 41%) but for patients without BRCA mutation (59% vs. 29%) [56].

Several phase II studies, including the PrECOG 0105 study, showed that different combinations with carboplatin may also be effective and may be considered as an alternative in patients with TNBC where an anthracycline-free NACT is appropriate [58].

In summary, the overlapping results of the central studies that added carboplatin to NACT highlighted the need to balance potential benefits with increased toxicity. While limited observational data demonstrate the efficacy of anthracycline-free regimens, it is necessary to expect to see evidence of RCTs. Data around optimal taxane use support the use of nab-paclitaxel instead of paclitaxel in limited clinical situations.

16.2.3.5 Investigational Approaches in the Neoadjuvant Setting

Several alternative strategies, including the contribution of additional chemotherapy drugs,

angiogenesis inhibitors, PARP inhibitors, immunotherapy, PI3KCA inhibitors, CDK4/6 inhibitors, are under investigation [59]. The usage of these agents outside of a well-designed clinical study is not recommended.

Response-Adjusted Sequential Therapy

It is standard to apply all planned chemotherapy before definitive surgery unless there is evidence of PD. "Response-adjusted sequential therapy" refers to the evaluation of the clinical response after the administration of a particular chemotherapy regimen in a number of cycles, followed by either continuation with the same treatment option, or switching to another non-cross-resistant chemotherapy, based on the response observed. This design allows independent evaluation of different drug regimens and individualization of the patient's treatment according to the interim response. Although the concept of "response-adjusted" therapy is attractive, it is still evolving as clinical data regarding its effectiveness in terms of the pCR rate and long-term outcomes are as yet inconclusive [60]. **Regarding the data compiled from studies testing this approach, response-adjusted sequential therapy is not recommended except for clinical trials.**

Experimental Approaches in HER2(+)BC

Concurrent administration of chemotherapy with HER2-targeted therapy is the standard of care, and the only strategy that had been shown to improve survival in HER2(+)BC thus remains the recommended approach for nearly all such patients. Several clinical trials are investigating the experimental approach of HER2-targeted therapies w/wo chemotherapy. For patients who refuse chemotherapy, or in whom comorbidities preclude the use of chemotherapy, or as part of clinical trials, there may be interest in considering non-chemotherapy combinations of HER2-targeted therapy. Other HER2-targeted biological agents such as lapatinib, T-DM1, and neratinib have been evaluated in the neoadjuvant setting, but none of these are superior to H(P) and have found a role in the standard approach [61].

16.2.4 Poor Response/PD During NACT

During NACT, less than 5% of patients will have PD. For patients who have progressed during NACT and are still operable, it is appropriate to stop NACT and to proceed with surgery. The indications for mastectomy and ALND after NACT are the same as for patients undergoing primary surgery. For patients who remain inoperable, the next line of chemotherapy should be considered to reduce the tumor mass and provide an opportunity for surgery.

16.2.5 Post-NACT Evaluation and Treatment

As soon as the patient has recovered from the toxicities of neoadjuvant therapy, definitive surgery should be performed within 3–6 weeks. This period is necessary for the recovery of the immune system of the patient.

16.2.5.1 Clinical Evaluation and Radiological Imaging After NACT

When NACT is completed, PE and the re-evaluation of the breast and axilla with US are usually sufficient. However, MRI can be performed to define the extent of disease better, to determine the optimal surgical approach. FDG-PET is not sensitive enough to detect residual disease. Tumor size correlation between PE, imaging (MMG, US, or MRI), and pathological examination is modest at best. All modalities suffered from a substantial percentage of over- and underestimation of tumor size and a low NPV of pCR [17].

The discordance in the clinicoradiological and pathological response depends on the different patterns of tumor shrinkage after NACT. 30–50% of patients with a cCR actually have residual cancer in the surgical specimen. On the contrary, approximately 20% of patients with clinicoradiological residual disease actually have a pCR. Therefore, pathologic assessment is the gold standard [62].

16.2.6 Adjuvant Treatment After NACT

16.2.6.1 Adjuvant Radiotherapy

For most patients receiving NACT, the indications for adjRT depend on the pre-treatment stage, and the type of surgery performed (BCS, mastectomy, etc.). Patients with residual breast and macroscopic nodal disease after NACT are treated with adjRT, based on retrospective evidence suggesting higher LoR rates in such patients. AdjRT is accepted for patients with stage III disease regardless of the response received, based on the retrospective data indicating that adjRT improves local control even in patients with pCR. For patients presenting with stage II, pre-treatment risk factors, as well as the tumor response to NACT, should be considered. Radiotherapy may be neglected in a selected group of patients with pCR [63].

16.2.6.2 Adjuvant Endocrine Treatment

Nearly all women with HR(+)HER2(−)BC will have residual disease after NACT. These patients should receive adjuvant ET alone, under the recommendations of current international guidelines.

16.2.6.3 Adjuvant Chemotherapy after NACT in Selected Patient Groups

For patients who have not completed NACT, the planned treatment should be continued in the adjuvant setting.

For most patients who have completed standard NACT, no additional adjCT is applied. However, the survival benefit from the use of capecitabine in women with HER2(−)BC who had residual disease after standard NACT containing anthracycline+/taxane, suggests that such patients may be suitable candidates for adjuvant capecitabine.

The investigators of the CREATE-X study randomized 900 patients with HER2(−)BC who had residual disease after NACT with anthracycline+/taxane, to two arms. Approximately one-third of the study population was TNBC. In one of the arms, patients received eight cycles of adjuvant capecitabine, while patients in the control arm did not receive adjChT. The final analysis showed that 5-year DFS (74% vs. 68%; [HR] 0.70) and OS (89% vs. 84%; [HR] 0.59) were longer in the capecitabine group than in the control group [64]. Subgroup analyses showed that among patients with TNBC, the rate of DFS was 69.8% in the capecitabine group versus 56.1% in the control group ([HR] 0.58), and the OS rate was 78.8% versus 70.3% ([HR] 0.52). However, side effects such as diarrhea, neutropenia, and hand-foot syndrome were higher in patients receiving capecitabine.

In preliminary results of a patient-level meta-analysis of 52 studies including 28,000 patients treated with NACT, achieving pCR was associated with improvements in both EFS and OS, irrespective of whether adjChT was administered [10]. Similarly, the randomized WGT-ADAPT trial failed to show the clinical benefit for the addition of adjuvant EC to patients with TNBC who achieve a pCR after a taxane-based NACT [65].

For patients achieving pCR following HER2-directed therapy HER2(+)BC, the benefit of adjChT has not been shown, but adjuvant trastuzumab (±pertuzumab), to complete a year of HER2-directed therapy, is recommended.

Patients who received NACT+H(P) with residual disease after surgical resection should receive 14 cycles of adjuvant T-DM1 [66]. In phase III, open-label, KATHERINE trial involving patients with HER2(+)eBC who were found to have residual invasive disease after NACT containing a taxane (w/wo anthracycline) and trastuzumab, patients were randomly assigned to receive adjuvant T-DM1 or trastuzumab for 14 cycles. The primary endpoint was iDFS. At the interim analysis, among 1486 randomly assigned patients the estimated iDFS at 3 years was 88.3% in the T-DM1 group and 77.0% in the trastuzumab group. iDFS was significantly higher in the T-DM1 group than in the trastuzumab group ([HR] 0.50). DiR occurred in 10.5% of patients in the T-DM1 group and 15.9% of those in the trastuzumab group. The safety data were consistent with the known safety profile of

Table 16.1 Neoadjuvant regimens for HER2(+) breast cancer [46]

Chemotherapy regimen	
4(dd) AC-12wPacH(P) 4(dd)AC-4TH(P)	Doxorubicin and cyclophosphamide (AC) every 2 (dose-dense; preferred approach) or 3 weeks for four cycles, followed by paclitaxel weekly for 12 weeks (wP) or docetaxel every 3 weeks for four cycles. Trastuzumab weekly for 12 weeks or every 3 weeks for four cycles is started concurrently with initiation of the taxane. If pertuzumab is added, it should also be started with the initiation of the taxane and given every 3 weeks for four cycles
12wPacH(P)-4(dd)AC 4TH(P)-4(dd)AC	The same treatments discussed above can be administered in the reverse order, which may cause less cardiotoxicity Note that trastuzumab (and pertuzumab, if added) is held during the AC portion of this treatment
6TCbH(P)	Docetaxel and carboplatin every 3 weeks for 6 cycles with concurrent trastuzumab, w/wo pertuzumab
18wPac(w) CbH(P)	Weekly paclitaxel with carboplatin, administered either every 3 weeks or weekly, with concurrent trastuzumab, w/wo pertuzumab, for 18 weeks
4FEC/EC-TH(P) or TH(P)-4FEC/EC	Fluorouracil, epirubicin, and cyclophosphamide (FEC) every 3 weeks for three to four cycles or epirubicin and cyclophosphamide (EC) every 3 weeks for four cycles are often used in place of AC in the above regimens in Europe. As with AC TH(P), trastuzumab w/wo pertuzumab is administered concurrently with the taxane only

T-DM1, with more AEs associated with T-DM1 than with trastuzumab. Among patients with HER2(+)eBC who had residual invasive disease after completion of neoadjuvant therapy, the risk of recurrence of invasive BC or death was 50% lower with adjuvant T-DM1 than with trastuzumab alone.

A treatment escalation is currently explored in the post-NACT setting with novel agents or combinations with platinum salts, PARP inhibitors, immune checkpoint inhibitors, and CDK4/6 inhibitors [67].

16.3 Conclusion

BC is a heterogeneous disease varying widely in histology, grade, proliferative rate, HR/HER2 status, and molecular/genetic features. Neoadjuvant treatment decisions should be made on multidisciplinary tumor boards for patients with early and locally advanced breast cancer. The escalation of adjuvant treatment has made neoadjuvant therapy an ethical obligation in high-risk HER2(+) and TNBC patients. In light of the current translational and clinical studies, treatment approaches continue to evolve, leading a paradigm shift in the future in selected patient groups (Table 16.1).

Tips and Tricks

Benefits of NACT

- Eradicates micrometastatic disease, prevents distant recurrences, and improves long-term outcomes and OS
- Downstages the tumor, allows BCS, improves cosmetic results, and reduces postoperative complications such as lymphedema, motion restriction, and postoperative pain syndromes
- Can convert inoperable tumors operable
- Provides prognostic information based on response to therapy, particularly in patients with HER2(+) and TNBC
- Guides the identification of predictive biomarkers specific to the tumor or the patient, regarding response or resistance to therapy
- Allows the modification or addition of "salvage" adjuvant regimens among patients with HER2(+) and TNBC with residual disease
- Allows time for genetic testing
- Allows time to plan breast reconstruction in patients electing mastectomy
- Offers a translational research platform to test de-escalation/escalation strategies

Opportunities
- May allow SLNB alone if positive axilla is cleared with therapy
- May provide an opportunity to modify systemic treatment if no preoperative therapy response or progression of the disease
- May allow for smaller radiotherapy ports or less radiotherapy if axillary nodal disease cleared
- Excellent research platform to test novel therapies and predictive biomarkers

Cautions
- Possible overtreatment with systemic therapy if the clinical stage is overestimated
- Possible undertreatment locoregionally with radiotherapy if the clinical stage is underestimated
- Possibility of disease progression during preoperative systemic therapy

Candidates for NACT
- **Patients with inoperable breast cancer:**
  - IBC
  - N2–N3 nodal disease
  - T4 tumors

Patients with operable breast cancer:
  - A high tumor-to-breast ratio in a patient who desires BCS
  - Suboptimal postoperative cosmetic outcome due to tumor size (T3, >5 cm) and location.
  - With N+ disease likely to become N0 with NACT
  - Intermediate to high-risk HER2(+) or TNBC (≥T2 and/or N+ tumors)

Patients with temporary contraindications to surgery:
  - Pregnant patients

Noncandidates for NACT
  - Patients with extensive in situ disease when the extent of invasive carcinoma is not well-defined
  - Patients with a poorly delineated extent of tumor
  - Patients whose tumors are not palpable or clinically assessable

Neoadjuvant therapy options
- Sequential anthracycline/taxane-based regimen is the standard for the majority of patients.
- EC or AC is standard for anthracycline-based regimens.
- Non-anthracycline regimens may be used in patients at risk of cardiac complications.
- The use of dose-dense schedules, with G-CSF support, should be considered, particularly in highly proliferative tumors.
- If NACT is used, all chemotherapy should be delivered preoperatively.

HER2(+)BC
- Patients with HER2(+) LABC (c-stage IIB [T3N0] or stage III) should receive neoadjuvant rather than adjuvant therapy to improve surgical options. This treatment may also be offered to patients with eBC, especially if the goal of treatment is to facilitate BCS or more limited ALND.
- Neoadjuvant trastuzumab should be given to all HER2(+)eBC patients who do not have contraindications for its use.
- Chemotherapy and dual anti-HER2 blockade associated with trastuzumab plus pertuzumab have shown significant improvements in the pCR rate, although a benefit in survival outcomes has not yet been demonstrated.
- For patients receiving an anthracycline-based regimen as part of their NACT, HER2-targeted therapy is administered concurrently with a taxane, either following or preceding anthracycline treatment.

- Less intensive and toxic chemotherapy regimens with trastuzumab may be substituted in patients with less extensive (c-stage I–IIA) disease, older patients, and those with significant comorbidities. TCbHP is the preferred regimen to avoid the risks and toxicities associated with anthracyclines.
- All patients treated with preoperative chemotherapy and HER2-targeted therapy should continue trastuzumab after surgery to complete a full year of trastuzumab treatment, even if the patient achieved a pCR with neoadjuvant therapy. There is no demonstrated long-term benefit for the administration of additional chemotherapy or of pertuzumab in the adjuvant setting.
- Postoperative treatment with ado-trastuzumab emtansine (T-DM1) would be considered if the patient were found to have residual invasive disease in the breast or axillary nodes following NACT with single or dual HER2-targeted therapy.

TNBC

- NACT is administered for women with TNBC ≥0.5 cm or N+ TNBC, regardless of tumor size.
- The addition of a platinum compound may be considered in TNBC and/or in patients with deleterious *BRCA1/2* mutations.
- In high-risk TNBC, not achieving pCR after standard NACT, the addition of 6–8 cycles of capecitabine postoperatively may be considered.

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