Neoadjuvant Chemotherapeutic and Targeted Therapies for Early-stage, High-risk Breast Cancer

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Abstract

Neoadjuvant or preoperative chemotherapy is the preferred treatment for locally advanced, inflammatory and early-stage high-risk breast cancers. Patients with locally advanced breast cancers are candidates for neoadjuvant therapy because their tumours are often not amenable to resection. On the other hand, patients are candidates for neoadjuvant chemotherapy if the breast-conserving surgery is not possible. At present, anthracycline- and taxane-based chemotherapy regimens remain as the cornerstone for neoadjuvant therapy in early breast cancer, but there is a clear need for effective therapies in high-risk, early-stage patients. A number of chemotherapeutic and targeted therapies have been evaluated in clinical trials with varying results. The US Food and Drug Administration (FDA) has recently approved pertuzumab in combination with trastuzumab and cytotoxic chemotherapy as a neoadjuvant therapy option for HER2-positive breast cancer. This article reviews the neoadjuvant chemotherapeutic and targeted therapies options for early-stage, high-risk breast cancer. Possible role of molecular subtyping in triple-negative breast cancer is also described.

Keywords

Neoadjuvant, triple-negative, locally advanced, inflammatory, breast cancer, HER2, molecular subtyping

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According to the World Health Organization (WHO), cancer-related mortalities reach 7.9 million worldwide each year.[1] Among women, breast cancer is one of the most common cancers globally. Despite advances in early detection and understanding on the molecular pathogenesis of breast cancer, approximately 30 % of patients with early-stage breast cancer experience recurrent disease.[2] Systemic treatment of breast cancer includes cytotoxic chemotherapy, endocrine (or hormonal) therapy and targeted therapy. These therapeutic agents are used in the adjuvant (post-surgical), neoadjuvant (pre-surgical) and metastatic settings.

Neoadjuvant therapy (also referred to as preoperative, pre-surgical, induction or primary systemic therapy) is the systemic treatment of breast cancer in the preoperative setting with curative intent. It was first evaluated more than 30 years ago for the treatment of locally advanced, inflammatory (a subtype of locally advanced breast cancer) and inoperable breast cancers.[3] It is now increasingly used in patients with operable disease.[3] The primary objective of the neoadjuvant therapy is to improve surgical outcomes[3–5] in patients for whom a primary surgical approach is technically not feasible and in patients with operable breast cancer who desire breast conservation. Second, neoadjuvant therapy decreases the need for complete axillary lymph node dissection.[6–8] It also allows an early evaluation of the systemic therapy. Third, neoadjuvant therapy gives clinicians an opportunity to obtain tumour specimens prior to and during the preoperative treatment, thus enabling researchers to investigate emerging drug therapies and predictive biomarkers.[7,8] Recently, following the announcement by the US Food and Drug Administration (FDA)[9] that it will consider neoadjuvant randomised trials for accelerated drug approval in early breast cancer, there has been a marked increase in clinical trials with novel agents in the neoadjuvant setting. This review focuses on the current and emerging neoadjuvant chemotherapies and targeted therapies for early-stage, high-risk[9] (defined as 20–25 % risk of recurrence or death at 5 years) breast cancer.

Patient Selection

Neoadjuvant chemotherapy is the preferred treatment for locally advanced and inflammatory breast cancer. According to the American Joint Committee on Cancer,[10] locally advanced breast cancer is a stage III disease. Clinically, locally advanced breast cancer includes tumours that are localised to the breast tissue without regional nodal involvement, and may also include tumour sizes greater than 5 cm in diameter, or tumours of any size with overlying oedema, chest-wall fixation, skin infiltration or inflammatory features. Among these forms of locally advanced breast cancer, only clinical stage IIIA (T0N2M0; T1-3N2M0) is considered surgically resectable; whereas clinical stage IIIB (T4N0-2M0) and stage IIIC (any TN3M0) are considered unresectable or inoperable.[11] Patients with locally advanced breast cancer IIIB-C are candidates for neoadjuvant therapy. Moreover, patients with high-risk, early-stage breast cancer (clinical stage I or II) are candidates for neoadjuvant therapy if breast-conserving surgery is not possible or if the tumour subtype is associated with a higher likelihood of response (e.g. human epidermal growth factor receptor type-2 [HER2]-positive or triple-negative [oestrogen receptor [OR]-negative, progesterone receptor [PR]-negative, HER2-negative), regardless of tumour size.[12,13]

The histologically proved complete response following neoadjuvant therapy, i.e. the absence of invasive and non-invasive tumour in the breast tissue and lymph nodes (ypT0ypN0), confirmed by pathology, is known as the pathological complete response (pCR).[10] It has been widely used as a surrogate marker for disease response and is an indication for complete eradication of distant micrometastasis or residual disease.[11] It was first observed in patients with locally advanced breast cancer[14] and was subsequently confirmed in randomised trials in patients with operable disease.[14] However, the definition of pCR and the methods of assessment varied across clinical trials.[15–22] Therefore, pCR alone cannot be applied as a predictor for long-term disease outcome. It is important to consider tumour involvement in both breast tissue and lymph nodes for pCR since the presence of residual disease in lymph nodes after neoadjuvant therapy may affect disease-free survival (DFS) and overall survival (OS).[23,24] Of note, ductal carcinoma *in situ* (DCIS) does not require pCR since the presence of residual disease in DCIS does not affect DFS or OS.[25,26]

Neoadjuvant chemotherapy for locally advanced breast cancer is generally anthracycline- or taxane-based (see *Table 1*). At present, approximately 20 % of patients[14–17,23] achieve pCR after an appropriate neoadjuvant regimen. Randomised trials[20,27] showed that non-anthracycline and anthracycline-containing regimens are considered equally efficacious regardless of whether they are given pre- or postoperatively. Equally, long-term efficacy had been demonstrated in the National Surgical Adjuvant Breast and Bowel Project (NSABP) trial in which docetaxel was administered either pre- or postoperatively.[28] An important caveat is, if the goal of therapy is to treat operable breast cancer, then any patient who is indicated for adjuvant therapy should also be offered neoadjuvant therapy.[14] Current US National Comprehensive Cancer Network (NCCN) guidelines[29] state that preoperative chemotherapy is not indicated unless invasive breast cancer is confirmed.

Cytotoxic Chemotherapy Principle and Options

In the last two decades, the potential benefits of preoperative (neoadjuvant) versus postoperative (adjuvant) chemotherapy have been tested in terms of DFS and OS. A recent meta-analysis[26] of nine randomised trials involving a total of 3,946 patients reported no differences in death, disease progression or distant recurrence between randomised arms. However, there is significant risk of locoregional recurrence after neoadjuvant chemotherapy, with odds ratio of 1.22 (95 % confidence interval [CI] 1.04–1.43). This significant risk is confined to trials with an excess of patients in the neoadjuvant arm that avoided surgery altogether, thus implicating that pCR is not a safe indicator for response since patients may proceed directly to radiation therapy. In fact, the NSABP B-27 trial[28] showed that, although pCR increased from 13.7 to 26.1 % ($p<0.01$) when four cycles of neoadjuvant docetaxel were added to four cycles of doxorubicin and cyclophosphamide (AC) alone (n=1,609), the rates on disease-free survival (DFS) and overall survival (OS) were no different in these two arms. Thus, broad acceptance of pCR as a long-term surrogate marker for DFS and OS requires formal comparison with parallel, conventional trials. The NSABP B-27 appears to challenge the validity of using a primary tumour response as the sole predictor for therapeutic effect. Nevertheless, improved pCR[29] has been demonstrated in certain subgroups (e.g. patients with triple-negative disease, HER2-positive disease or receiving targeted therapies).

Interestingly, the role of some non-traditional agents (e.g. capecitabine, gemcitabine) was studied in taxane and anthracycline-based regimens. In the GeparQuattro trial,[30] 1,421 patients received four cycles of neoadjuvant epirubicin and cyclophosphamide (EC) were randomised to: (1) four cycles of docetaxel; (2) four cycles of docetaxel and capecitabine; and (3) four cycles of docetaxel followed by capecitabine. Results demonstrated that concurrent (but not sequential) treatment of docetaxel and capecitabine did not lead to significant improvement in pCR or breast-conservation rates. There was increased toxicity such as diarrhoea, nail changes and hand–foot syndrome. In general, poor or non-responders to the first-line taxane or anthracycline-based regimens are either switched to second-line chemotherapy or proceed directly to surgery. However, even with a pCR, surgery is still indicated, since the risk of residual microscopic disease is high.[4,7]

The NSABP B-18 trial[5] is the largest trial to date to investigate neoadjuvant chemotherapy. A total of 1,523 patients with T1 to T3 and N0 to N1 disease were randomised to receive preoperative AC versus postoperative AC for four cycles. In addition to using traditional response criteria, patients who had a complete response also underwent histology analysis for pCR. After a 9-year follow-up, investigators reported no significant difference in DFS and OS between these two groups. Furthermore, there was a significant association between pCR and outcome: patients with a pCR had a 50 % reduction in the risk of death compared with the overall population (relative risk 0.5, 95 % CI 0.32–0.78). The rate of pCR was higher in the group of AC added with docetaxel compared with the AC group (26.1 % versus 12.9 %; $p<0.0001$).[5]

The effect of weekly paclitaxel versus the standard every-3-week paclitaxel was evaluated in a phase III randomised trial.[31] Results showed that weekly paclitaxel had a statistically significant benefit in improvement of pCR compared with every-3-week paclitaxel. For N1 patients, the pCR was 28 % with weekly paclitaxel compared with 13.7 % with every-3-week paclitaxel (see *Table 2*).

Neoadjuvant Therapy for Early-stage, High-risk Breast Cancer

Recently, a meta-analysis of the Collaborative Trials in Neoadjuvant Breast Cancer (CTNeoBC) by Cortazar and colleagues[32] suggested that patients who attain pCR have a more favourable long-term outcome such as event-free survival (EFS) and OS. The association of pCR with EFS and OS is stronger in patients with aggressive tumour types (HER2-overexpressed disease and triple-negative tumours) compared with the less-aggressive tumour types (hormone receptor-positive and low-grade tumours). However, the magnitude of pCR improvement is not predictive of long-term clinical benefit, possibly due to low pCR rates, the heterogeneity of the population or the lack of correlation between pCR and EFS and OS. In a recent meta-analysis[33] of seven randomised trials in 6,377 patients with primary breast cancer who received anthracycline- and taxane-based neoadjuvant chemotherapies, pCR is a good surrogate endpoint for patients with triple-negative, HER2-negative disease.

Triple-negative Disease

Breast cancer is a heterogeneous disease. Based on the expression of OR, PR and HER2, gene expression profiling has identified four distinct malignant subtypes: basal-like, HER2-enriched, luminal A and luminal B. Luminal A and B subtypes account for 70 % of all breast cancers and are hormone-receptor-positive.[34] In particular, luminal A is hormone receptor-positive and HER2-negative whereas luminal B is both hormone receptor-positive and HER2-positive. Among these subtypes, triple-negative breast cancer (TNBC) is characterised by OR, PR and HER2 negativity. It accounts for 10–20 % of all breast cancers and is diagnosed more frequently in younger individuals, those with *BRCA1* gene mutations and African American/Hispanic women.[35] Recent

Table 1: Common Cytotoxic Chemotherapy and Targeted Therapies in the Neoadjuvant Setting for Early Breast Cancer

Regimen	Dosing/Route/Schedule	Note	Study Group/Author
AT → T → CMF + H	Doxorubicin 60 mg/m² i.v. Paclitaxel 150 mg/m² i.v. every 3 weeks for 3 cycles Paclitaxel 175 mg/m² i.v. every 3 weeks for 4 cycles Cyclophosphamide 600 mg/m² i.v. Methotrexate 40 mg/m² i.v. Fluorouracil 600 mg/m² i.v. on days 1 and 8 every 4 weeks for 3 cycles Trastuzumab loading dose 8 mg/kg i.v. for 90 minutes; 6 mg/kg i.v. for 30 minutes every 3 weeks for 10 cycles	Trastuzumab could be given every 4 weeks during CMF For HER2-positive locally advanced or inflammatory BC	Gianni et al. 2010[48]
DAC x 6	Docetaxel 75 mg/m² i.v. Doxorubicin 50 mg/m² i.v. Cyclophosphamide 500 mg/m² i.v. Every 3 weeks x 6 cycles	HER2-negative BC	Von Minckwitz et al. 2005[67]
AT x 4	Doxorubicin 60 mg/m² i.v. Paclitaxel 200 mg/m² i.v. Every 3 weeks x 4 cycles	HER2-negative BC	Dieras et al. 2004[68]
EC → D + H	Epirubicin 90 mg/m² (day 1) i.v. Cyclophosphamide 600 mg/m² (day 1) i.v. Every 3 weeks for 4 cycles Docetaxel 100 mg/m² (day 1) i.v. Every 3 weeks for 4 cycles Trastuzumab loading dose 8 mg/kg i.v. on day 1 of first EC cycle; then 6 mg/kg i.v. every 3 weeks with concomitant cytotoxic therapy	HER2-positive BC	Untch et al. 2010[50]
EC → DB	Epirubicin 90 mg/m² (day 1) i.v. Cyclophosphamide 600mg/m² (day 1) i.v. Every 3 weeks for 4 cycles Docetaxel 100 mg/m² (day 1) i.v. Every 3 weeks for 4 cycles Bevacizumab 15 mg/kg (day 1) i.v. every 3 weeks for 4 cycles starting on day 1 of first EC cycle	Triple-negative BC	Gerber et al. 2013[41]
Weekly T	Paclitaxel 80 mg/m² i.v. weekly x 12 weeks	Hormone-receptor positive and negative BC	Green et al. 2005[31]
AC → D	Doxorubicin 60 mg/m² i.v. Cyclophosphamide 600 mg/m² i.v. Every 3 weeks x 4 cycles Docetaxel 100 mg/m² i.v. every 3 weeks x 4 cycles	OR-negative had higher response	Bear et al. 2004[28]

A = doxorubicin; B = bevacizumab; BC = breast cancer; C = cyclophosphamide; D = docetaxel; E = epirubicin; F = fluorouracil; H = trastuzumab; HER2 = human epidermal growth factor receptor type II; i.v. = intravenously; M = methotrexate; T = paclitaxel; OR = oestrogen receptor.

studies suggest that there is significant overlap between the TNBC and the basal-like subtype, but TNBC displays heterogeneous patterns in morphological, genetic, immunophenotypic and clinical features.[36–38] In general, TNBC is associated with a poor prognosis of increased relapse and decreased OS.[39] At present, there is no targeted therapy available for TNBC. Cytotoxic chemotherapy, specifically anthracycline- and taxane-based regimens, remains as the current standard.[14] The aggressive nature of TNBC may be due to an increased expression of vascular endothelial growth factor (VEGF), which contributes to increased tumour proliferation through angiogenesis.[40]

In the multicentre GeparQuinto study,[41] researchers investigated the use of bevacizumab with chemotherapy in the neoadjuvant setting for patients with TNBC. The primary objective was to measure the pCR after neoadjuvant chemotherapy with or without bevacizumab (B). All patients received epirubicin (E) 90 mg/m² plus cyclophosphamide (C) 600 mg/m² every 3 weeks for four cycles, followed by four, 3-week cycles of docetaxel (D) 100 mg/m². Patients were then randomised to receive either eight cycles of bevacizumab (B) 15 mg/kg of body weight intravenously (i.v.) every 3 weeks starting on day 1 of the first EC cycle (EC-DB) or no additional treatment (EC-D). A total of 663 TNBC patients were included in the study. Results showed that only 95 patients (27.9 %, 95 % CI 23.2–33.0) who received EC-D achieved pCR, whereas 127 patients (39.3 %, 95 % CI 34.0–44.9) who received EC-DB achieved pCR (p=0.003). Thus, addition of bevacizumab to the neoadjuvant anthracycline–taxane-containing chemotherapy significantly increased the pCR rate from 27.9 % to 39.3 % in patients with operable or locally advanced TNBC (except T4 tumours). However, the rate of breast-conservation surgery was similar between the two groups (EC-D: 75 %; EC-DB: 72 %; p=0.441) and was not considered statistically significant. Addition of bevacizumab also resulted in increased adverse effects such as febrile neutropenia, mucositis, hand–foot syndrome, infection and hypertension compared with chemotherapy. Of note, the GeparQuinto study included an analysis of other definitions of pCR to mitigate the inconsistencies in defining pCR from other studies.

Furthermore, in a phase II, multicentre, open-label, single-arm trial,[42] the efficacy and safety of neoadjuvant bevacizumab combined with

Table 2: Summary of Major Clinical Trials in Neoadjuvant Breast Cancer Treatment

Trial Name	Important Conclusion/Note	Reference
NSABP B-27	Non-anthracycline and anthracycline-containing regimens are considered equally efficacious regardless of given pre- or postoperatively	28
GeparQuattro trial	Concurrent (but not sequential) treatment of docetaxel and capecitabine did not lead to a significant improvement in pCR or breast-conservation rates Increased toxicity such as diarrhoea, nail changes and hand–foot syndrome	30
NSABP B-18 trial	No significant difference in disease-free survival and overall survival between pre- and postoperative doxorubicin and cyclophosphamide (AC) Rate of pCR was higher in the group of AC added with docetaxel (26.1 % versus 12.9 %; p<0.0001)	5
Weekly versus q 3-week paclitaxel	Weekly paclitaxel had a statistically significant benefit in improvement of pCR compared with every-3-week paclitaxel	31
GeparQuinto trial	Addition of bevacizumab increased the pCR rate from 30.9 % to 41.8 % (p=0.004) Addition of bevacizumab resulted in increased adverse effects such as febrile neutropenia, mucositis, hand–foot syndrome, infection and hypertension compared with chemotherapy Bevacizumab was added after 4 cycles of epirubicin–cyclophosphamide and before surgery in triple-negative BC patients	41
BEVERLY-2 trial	Neoadjuvant bevacizumab combined with trastuzumab and chemotherapy for HER2-positive inflammatory breast cancer was safe and effective (63.5 % pCR, 95 % CI 49.4–77.5)	42
NOAH trial	Neoadjuvant and adjuvant trastuzumab be considered for HER2-positive locally advanced or inflammatory BC to improve EFS, OS and pCR	48
Neosphere trial	Clinical response and overall response were greatest in the pertuzumab, trastuzumab and docetaxel group (Group B)	49
NeoALLTO	pCR rate achieved statistical significance in the lapatinib and trastuzumab combination compared to trastuzumab (51 % versus 29.5 %, respectively; p=0.0001) No major cardiotoxicity. Toxicity included mostly diarrhoea and liver enzyme alterations	45
NSABP protocol B-41	Combined HER2-therapy (lapatinib and trastuzumab) produced a numerically but insignificantly higher pCR rate than single-agent HER2 therapy	46
Tryphaena trial	Combination of neoadjuvant trastuzumab, pertuzumab and standard chemotherapy (given concurrently or sequentially with anthracycline-based regimen or given sequentially with carboplatin-based regimen) is safe	53
Dose-dense AC or sequential AC for triple-negative BC	Both regimens showed equivalent pCR (16 % versus 12 %) Dose-dense regimen yielded statistically non-significant higher pCR rate (48 % versus 24 %; p=0.087) than the conventional sequential regimen DFS was statistically higher for triple-negative than non-triple-negative patients (p=0.019)	64
NSABP-40	HR-positive subset had a statistically significant incremental increased response in pCR with the addition of bevacizumab (11.1 % without bevacizumab versus 16.8 % with bevacizumab; p=0.03) than HR-negative patients T4 tumours were excluded and bevacizumab was administered for the first 6 cycles only Addition of capecitabine or gemcitabine did not increase the rate of pCR	43

AC = cyclophosphamide-anthracycline regimen; BC = breast cancer; CI = confidence interval; DFS = disease-free survival; EFS = event-free survival; HER2 = human epidermal growth factor receptor type II; HR = hormone receptor; OS = overall survival; pCR = pathological complete response.

trastuzumab and chemotherapy in 52 women (age equal to or greater than 18 years) with primary HER2-positive inflammatory breast cancer were evaluated. Results demonstrated that 33 (63.5 %, 95 % CI 49.4–77.5) patients had a pCR. The most common adverse events were asthenia and nausea (69 %) and grade 3–4 neutropenia (48 %). Only one grade 3 or worse adverse event related to bevacizumab was reported (hypertension, one patient). Four patients (8 %) had cardiac failure. Thus, neoadjuvant chemotherapy for inflammatory breast cancer seemed to be efficacious and tolerated. Further study of bevacizumab is warranted.

In a study (NSABP-40) conducted by Bear and colleagues,[43] 1,206 HER-2 negative breast cancer patients were randomised 1:1:1 to: (1) docetaxel 100 mg/m^2 i.v. on day 1 of each 21-day cycle for four cycles; followed by four cycles of doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 (AC) i.v. every 3 weeks; (2) capecitabine 825 mg/m^2 orally twice a day on days 1 to 14 with docetaxel 75 mg/m^2 i.v. on day 1, followed by the AC chemotherapy; (3) gemcitabine 1,000 mg/m^2 i.v. on days 1 and 8 and docetaxel 75 mg/m^2 i.v. on day 1, followed by the AC chemotherapy. Patients were also randomly assigned to receive or not to receive bevacizumab (15 mg per kilogram of body weight) for the first six cycles of chemotherapy. The primary endpoint was the rate of pCR that was defined as the absence of histological evidence of invasive tumour cells in the surgical specimen.

Results demonstrated that the addition of capecitabine or gemcitabine did not increase the rate of pCR, and there was no significant difference among the three chemotherapy regimens. This negative result was not surprising since similar findings had been reported in the GeparQuattro trial[30] and another study.[44] Furthermore, subgroup analyses of tumour size, nodal status, hormonal receptor status, age and tumour grade did not show significant differences between the three chemotherapy regimens. Notably, patients in the hormone receptor-positive subset had a statistically significant incremental increase in pCR with the addition of bevacizumab (11.1 % without bevacizumab versus 16.8 % with bevacizumab; p=0.03) than patients in the hormone receptor-negative subset. This result was in contrast to the German GeparQuinto study[41] in which the TNBC (hormone receptor negativity was defined by less than 10 % of immunostaining) patients had a significant pCR rate with bevacizumab. In addition, in the GeparQuinto trial, bevacizumab was added after four cycles of EC and before surgery. But in the NSABP-40 study, patients with T4 tumours were excluded and bevacizumab was administered for the first six cycles only.

Further analysis of the NSABP-40 study showed that the rate of pCR was significantly increased when bevacizumab was added to the docetaxel-capecitabine regimen (36.1 % versus 23.5 %; p=0.009). However,

bevacizumab use was associated with increased rates of hypertension, mucositis, hand–foot syndrome and a statistically significant increase in grade 3 and 4 left ventricular dysfunction (<1 % versus 1 %; p=0.02). To conclude, the use of anti-VEGF agent must be balanced by its risk–benefit ratio and current use cannot be recommended outside of clinical trials. Long-term study is warranted to determine if there is any significant improvement in OS.

HER2 Targeted or Directed Therapy

For patients with HER-2 positive breast cancer, current FDA approved neoadjuvant therapy options include: (1) trastuzumab and pertuzumab in combination with cytotoxic chemotherapy; (2) trastuzumab as a single agent or in combination with cytotoxic chemotherapy. Lapatinib, a dual HER2/EGFR tyrosine kinase inhibitor, currently FDA approved for metastatic therapy, had been used preoperatively in combination with trastuzumab in clinical trials.[45,46] In standard neoadjuvant therapies for HER2-positive breast cancer, trastuzumab is typically combined with the taxane portion of systemic therapy, given the increased risk of cardiac toxicity when combined with anthracyclines. Nonetheless, a trial from MD Anderson Cancer Center in the US demonstrated the safe addition of epirubicin to trastuzumab.[47] Of note, the combination of anthracycline and anti-HER2 therapy is a labelled warning in the US and such combination cannot be used outside of clinical trials.

In an international, open-label, phase III trial (NOAH),[48] researchers evaluated the EFS in patients with HER-2 positive disease with or without trastuzumab therapy. Patients with locally advanced, HER-2 positive disease received neoadjuvant doxorubicin 60 mg/m^2 with paclitaxel 150 mg/m^2 every 3 weeks for three cycles, followed by paclitaxel 175 mg/m^2 administered every 3 weeks for four cycles. Cyclophosphamide 600 mg/m^2, methotrexate 40 mg/m^2 and fluorouracil 600 mg/m^2 were then given on days 1 and 8 every 4 weeks for three cycles. A total of 118 patients were randomised to receive chemotherapy alone and 117 patients were randomised to receive concomitant trastuzumab therapy. Additionally, the study design was amended to include HER-2 negative patients, for which 99 patients were enrolled to receive chemotherapy alone. The 3-year EFS was statistically significant for the addition of trastuzumab (71 %, 95 % CI 61–78; n=36 events) as opposed to without trastuzumab (56 %, 95 % CI 46–65; n=51 events). Forty-five patients who received trastuzumab achieved a total pCR in breast and axillary nodes versus only 23 patients who achieved a total pCR without trastuzumab (p=0.001). The overall response rate was statistically significant for the use of trastuzumab (102 patients versus 87 patients; p=0.009). The researchers concluded that neoadjuvant and adjuvant trastuzumab should be considered for women with HER2-positive locally advanced or inflammatory breast cancers to improve EFS, OS and pathological tumour responses.

Another approach in managing HER-2 positive disease is through the use of dual HER-2 targeted therapies. Since pertuzumab binds to a different epitope from trastuzumab and sterically blocks the HER2 receptor from dimerisation with HER1, HER3 and HER4, combination therapy of pertuzumab and trastuzumab theoretically results in a more complete blockade of the HER2 signalling pathway than either agent alone. In the Neosphere trial,[49] 608 women with locally advanced, inflammatory or early HER-2 positive breast cancer were enrolled. Investigators evaluated the role of pertuzumab in combination with trastuzumab in the neoadjuvant setting. Patients with confirmed HER2-positive were randomised into one of four neoadjuvant treatment arms: (1) trastuzumab plus docetaxel (group A); (2) pertuzumab and trastuzumab and docetaxel (group B); (3) pertuzumab and trastuzumab (group C); (4) pertuzumab plus docetaxel (group D). The primary endpoint was the pCR, which was defined as the absence of invasive neoplastic cells at microscopic examination of the primary tumour at surgery; remaining *in situ* lesions were allowed. Secondary outcomes were clinical response rate, time to clinical response, breast-conserving surgery rate and safety.

pCR was observed in 31 out of 107 patients in group A (29 %, 95 % CI 20.6–38.5), while 49 out of 107 patients in group B (45.8 %, 95 % CI 36.1–55.7) achieved pCR: this was statistically significant (p=0.0141). Eighteen patients and 23 patients achieved pCR in groups C (16.8 %, 95 % CI 10.3–25.3) and D (24 %, 95 % CI 15.8–33.7), respectively. Clinical response and overall response were greatest in the pertuzumab, trastuzumab and docetaxel group (Group B). Alopecia, neutropenia, diarrhoea, nausea, fatigue, rash, mucosal inflammation, myalgia, asthenia and headache were the most common adverse effects. Most common adverse effects of grade 3 or greater were neutropenia, febrile neutropenia and leucopenia. One patient in group A and three in group B experienced a left ventricular ejection fraction (LVEF) decline of 10–15 % to less than 50 % compared with baseline. One patient in groups C and D had decrease of greater than 15 % from baseline to an LVEF of less than 50 %.

NeoALLTO[45] was a phase III randomised trial that investigated the efficacy of neoadjuvant paclitaxel administered with either lapatinib, trastuzumab or conconcurrent lapatinib and trastuzumab in HER-2 positive breast cancer patients. pCR rate achieved statistical significance in the lapatinib and trastuzumab combination compared with trastuzumab (51 % versus 29.5 % respectively; p=0.0001). No major cardiotoxicity was observed in the neoadjuvant therapy. Toxicity included mostly diarrhoea and liver enzyme alterations.

On the contrary, a recent open-label, randomised phase III trial[46] (NSABP protocol B-41) suggested that combined HER2-targeted therapy (lapatinib and trastuzumab) in the neoadjuvant setting produced a numerically but insignificantly higher pCR rate than single-agent HER2-directed therapy. Dual-HER2 neoadjuvant therapy necessitates long-term study to determine if it results in significant improvement in OS compared with single HER2 therapy.[50,51]

The tolerability, especially cardiac safety, of neoadjuvant pertuzumab and trastuzumab with anthracycline-containing or anthracycline-free standard chemotherapy was evaluated in a randomised, open-label, multicentre phase II study[52,53] (Tryphaena trial). Two hundred and twenty-five patients with operable, locally advanced or inflammatory HER2-positive breast cancer were randomised 1:1:1 to receive six neoadjuvant cycles every 3 weeks (arm A: fluorouracil, epirubicin, cyclophosphamide [FEC] for three cycles followed by docetaxel [T] for three cycles; with trastuzumab and pertuzumab given concurrently throughout all six cycles; arm B: FEC x three cycles, followed by docetaxel and trastuzumab and pertuzumab for three cycles; arm C: docetaxel, carboplatin and trastuzumab (TCH) plus pertuzumab x six cycles total). Following neoadjuvant therapy, patients underwent surgery and continued trastuzumab to complete 1 year of adjuvant therapy. They received further adjuvant treatment (radiation, chemotherapy, hormonal therapy) according to local guidelines. The pCR rate was 61.6 %, 57.3 % and 66.2 %, respectively, for arm A, arm B and arm C. Both OR-positive and tumour-negative patients achieved high pCR rates (46–50 % range versus 65–84 % range, respectively).

During neoadjuvant therapy, two patients (2.7 % arm B) experienced symptomatic left ventricular systolic dysfunction and 11 patients (from all arms; arm A: 4 [5.6 %]; arm B: 4 [5.3 %]; arm C: 3 [3.9 %] had decline in LVEF of more than 10 % from baseline to less than 50 %. Thus, combination therapy of neoadjuvant trastuzumab and pertuzumab and standard chemotherapy (given concurrently or sequentially with anthracycline-based regimen or given sequentially with carboplatin-based regimen) is safe.

Taken together, neoadjuvant trastuzumab and pertuzumab combination is effective for HER2-positive breast cancer. Interestingly, HER2-positive patients have a relatively high rate of pCR to neoadjuvant chemotherapy, especially in those patients who also harbour tumour-negative tumours, reflecting the aggressive nature of these tumours.[54,55]

Future Directions

There is growing interest in targeting drug therapies based on specific signalling pathways for personalised medicine, e.g. neratinib, an investigational second-generation tyrosine kinase inhibitor that inhibits both EGFR (HER1) and HER2 signalling, is being assessed for its role in neoadjuvant chemotherapy with paclitaxel and trastuzumab[54] (NCT01008150 or NSABP FB-7 trial). EGFR antagonists, such as cetuximab, are being studied in combination with ixabepilone versus ixabepilone monotherapy (NCT01097642) in the preoperative setting of TNBC.[55] The recent FDA approval of the novel antibody drug conjugate, ado-trastuzumab emtansine (Kadcyla®, Genentech Inc., US) is being explored for its preoperative role with or without hormonal therapy versus other therapies[56] (e.g. ado-trastuzumab emtansine plus hormonal therapy versus ado-trastuzumab emtansine single agent versus trastuzumab plus hormonal therapy) in hormone receptor-positive and HER2-positive patients. These trials are likely to shed some light on how to effectively utilise the targeted neoadjuvant therapies for breast cancer.

About 20–40 % of inflammatory breast cancers are triple-negative.[57] TNBC tumours have a highly varied prognosis and clinical outcome, which may be a reflection of the different numbers of subgroups that have been identified through gene expression profiling.[58] Many researchers postulated that the high percentage of TNBC is one of the reasons that inflammatory breast cancer has been associated with a more aggressive clinical course and decreased OS.[59] Recently, Lehmann and colleagues[60] proposed that TNBC can be classified into six or seven subtypes based on differential gene expressions and gene ontologies: basal-like 1 and 2 (BL1, BL2), immunomodulatory (IM), mesenchymal (M), mesenchymal stem-like (MSL), luminal androgen receptor (LAR) and unstable (UNS). Of note, the LAR subtype (i.e. molecular apocrine) has been demonstrated to have a gene expression profile resembling that of hormone receptor-positive tumours, and this signalling pathway may be attributable to the androgen receptor.[61] Furthermore, emerging data suggest that some breast cancer subtypes, including triple-negative tumours, may be sensitive to neoadjuvant dose-dense alkylating agent-based chemotherapy.[62] Of note, the subtypes proposed by Lehmann were validated by a recent study by Masuda and colleagues[63] in 146 TNBC patients. In this study, they demonstrated a statistically significant association between the TNBC subtype and the pCR status (p=0.04379). The BL1 subtype had the highest pCR rate (52 %) while the BL2 and LAR subtypes had the lowest (0 % and 10 %, respectively) pCR rates. Further studies to investigate whether such molecular subtyping could translate into a long-term clinical benefit for TNBC patients are underway.

Recently, Giachetti and colleagues[64] compared the efficacy of two different neoadjuvant regimens, either a dose-dense cyclophosphamide-anthracycline regimen (n=99) or a sequential administration of cyclophosphamide and anthracycline, followed by taxanes (EC-T) regimen (n=168) in a total of 267 patients with locally advanced breast cancers. Although these two regimens showed equivalent pCR (16 and 12 %, respectively), the dose-dense regimen yielded a statistically non-significant higher pCR rate than the conventional EC-T (48 % versus 24 %, p=0.087) regimen. Triple-negative tumours represented 23 % and 25 % of cases, respectively. DFS was statistically higher for triple-negative than for non-triple-negative patients (p=0.019). Toxicities associated with the dose-dense regimen were manageable despite pronounced bone marrow toxicity. Thus, dose-dense neoadjuvant chemotherapy may be associated with a favourable survival in TNBC patients. Apparently, more studies are needed for the dose-dense regimens in the locally advanced tumours.

In addition, based on the molecular subtyping proposed by Lehmann as previously discussed, a subset of TNBC depends on androgen signalling for growth (i.e. the molecular apocrine subtype). Drug therapies that inhibit androgen signalling are undergoing clinical trials to investigate their efficacy in this breast cancer subtype.[65] Last but not least, researchers were able to show that although there is limited evidence that a subset of TNBC patients with *BRCA1* mutations may be sensitive to cisplatin, neoadjuvant cisplatin therapy cannot be recommended outside of a clinical trial. Multiagent neoadjuvant chemotherapy remains as the current mainstay for therapy of TNBC.[66-68]

Summary and Conclusion

Preoperative or neoadjuvant chemotherapy should be considered for women with high-risk, early-stage breast cancer (clinical stage I or II) as well as locally advanced and inflammatory breast cancers. A number of therapeutic agents have been evaluated as single agents and as part of the combination regimen, with varying results. The FDA has approved the neoadjuvant indication of pertuzumab with trastuzumab and systemic cytotoxic chemotherapy. More studies or confirmatory trials of the neoadjuvant dual-HER2 therapy will likely determine if there is a significant improvement in OS. There is also emerging evidence that molecular subtyping may help to individualise drug therapies in TNBC. ■

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