Review

Recent advances in systemic therapy

Advances in neoadjuvant (primary) systemic therapy with cytotoxic agents

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Abstract

Neoadjuvant therapy, also known as primary, induction, or preoperative therapy, is defined as the first systemic treatment a patient receives after cancer is diagnosed and indicates that subsequent therapies are intended. It was first used in the early 1970s for the treatment of inoperable locally advanced or inflammatory breast cancer. Based on a large body of clinical evidence and on the fact that primary breast cancer is today considered a systemic disease with a locoregional component, primary systemic therapy is now increasingly considered for women with operable disease for reducing mortality with lower toxicity, improving surgical options, and acquiring early information on response and biology of the disease.

According to the recommendations of an international expert panel on the use of primary systemic therapy (PST) of operable breast cancer, a PST with cytotoxic agents is preferred when breast-conserving surgery (BCS) is not possible or is likely to be suboptimal in terms of the cosmetic results or in patients whose tumors express markers of good response to chemotherapy such as low or absent hormone receptor status, high grade, and non-lobular invasive histology [1]. At least six cycles should be administered over the course of 4 to 6 months before surgery [1].

Preoperative endocrine therapy may be effective but its use as PST alone is appropriate mainly for frail postmenopausal patients or elderly patients in whom surgery would carry increased risk due to the advanced age or comorbidities of the patient [2]. Until now, there have been no data that accurately define which patients with estrogen receptor (ER)-positive disease benefits from neoadjuvant chemotherapy and for whom endocrine therapy would be sufficient. Current research efforts aim to identify molecular markers at surgery which predict long-term efficacy of neoadjuvant/adjuvant endocrine treatment.

Induction of a pathologic complete response (pCR) should be one of the primary goals of neoadjuvant therapy because patients with no evidence of tumor cells in the breast or in the lymph nodes after treatment may have a longer disease-free survival (DFS) and overall survival (OS) [3]. Before any PST is started, a core biopsy should be performed to confirm the diagnosis of invasive cancer and to obtain predictive markers such as histological subtype, tumor grading according to Elston and Ellis, ER and progesterone receptor status, and HER2 status [1].

Experiences from clinical studies

A number of clinical trials have evaluated the role of neoadjuvant chemotherapy for breast cancer. One of the pioneering studies for the PST concept was the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-18, which randomly assigned 1,523 women with operable breast cancer to receive four cycles of adriamycin and cyclophosphamide (AC) either before or after definitive surgery. In the group treated with preoperative chemotherapy, a rate of pCR, defined as the absence of residual malignant cells at the site of the primary tumor irrespective of the status of axillary nodes, of 13% was observed, with a significantly higher rate of breast conservation compared with surgery first (67%

AC = adriamycin and cyclophosphamide; AC-DOC = adriamycin and cyclophosphamide with docetaxel; ADOC = doxorubicin and docetaxel; AGO = Arbeitsgemeinschaft Gynäkologische Onkologie; AT = doxorubicin and paclitaxel; AT-CMF = doxorubicin and paclitaxel with cyclophosphamide, methotrexate, and 5-fluorouracil; BCS = breast-conserving surgery; cCR = clinical complete response; CI = confidence interval; CMF = cyclophosphamide, methotrexate, and 5-fluorouracil; DFS = disease-free survival; DOC = docetaxel; EC = epirubicin and cyclophosphamide; ER = estrogen receptor; GBG = German Breast Group; HR = hazards ratio; iv = intravenous; NSABP = National Surgical Adjuvant Breast and Bowel Project; NX = vinorelbine and capecitabine; OS = overall survival; pCR = pathologic complete response; PST = primary systemic therapy; TAC = docetaxel, doxorubicin, and cyclophosphamide.

versus 60%; $P = 0.002$), especially in patients with tumors larger than 5 cm in diameter [4].

At a median follow-up of 9 years, comparison between the groups treated with neoadjuvant and with adjuvant therapies revealed no statistically significant overall differences in either DFS or OS [5]. However, a statistically significant correlation was shown between primary tumor response and outcome: individuals achieving a pCR experienced significantly improved outcomes compared with non-pCR subjects, including 9-year DFS (75% versus 58%) and OS (85% versus 73%), and a 50% decrease in the risk of death compared with all other pathologic markers (relative risk 0.50, 95% confidence interval [CI] 0.32 to 0.78).

In a similar study design, the European Organization for Research and Treatment of Cancer (EORTC) randomly assigned 698 women to anthracycline-based chemotherapy before or after surgery [6]. As shown in the NSABP B-18 trial, there was no significant difference in terms of OS (hazards ratio [HR] 1.16; $P = 0.38$), progression-free survival (HR 1.15; $P = 0.27$), or time to locoregional recurrence (HR 1.13; $P = 0.61$) at a median follow-up of 56 months. Fifty-seven patients (23%) were downstaged by the preoperative chemotherapy, whereas only 14 women (18%) underwent mastectomy and not the planned breast-conserving therapy.

To examine the role of neoadjuvant taxane, the NSABP randomly assigned 2,411 women in study B-27 to neoadjuvant AC alone, to neoadjuvant AC followed by docetaxel before surgery, or to neoadjuvant AC followed by adjuvant docetaxel after surgery. Compared with preoperative AC alone, preoperative AC followed by docetaxel increased the clinical complete response (cCR) rate (40.1% versus 63.6%; $P < 0.001$), the overall clinical response rate (85.5% versus 90.7%; $P < 0.001$), the pCR rate (13.7% versus 26.1%; $P < 0.001$), and the proportion of patients with negative nodes (50.8% versus 58.2%; $P < 0.001$) [7]. Pathologic primary breast tumor response was a significant predictor of pathologic nodal status ($P < 0.001$). At a median follow-up of 6.5 years, women achieving pCR demonstrated significantly improved survival compared with those without pCR (HR 0.33, 95% CI 0.23 to 0.47; $P < 0.0001$) [8].

In the European Cooperative Trial in Operable breast cancer (ECTO), women with operable breast cancer (primary tumor greater than 2 cm) were randomly assigned to adjuvant doxorubicin (75 mg/m^2 every 21 days) for four cycles followed by CMF (cyclophosphamide, methotrexate, and 5-fluorouracil) or to adjuvant doxorubicin (60 mg/m^2) and paclitaxel (200 mg/m^2 over the course of 3 hours every 21 days) for four cycles followed by CMF (AT-CMF) or to AT-CMF as PST, yielding a cCR in 52% of patients (27% after AT and 25% more after CMF) [9]. pCR was documented in 23% of specimens and was associated with negative axillary nodes in 87%. Conservative surgery was more frequent after PST (71% versus 35% before adjuvant therapy; $P < 0.00001$) regardless of tumor size at diagnosis. The frequency of pathologically negative nodes was also significantly higher in the PST group (61% versus 38%).

During the same meeting, the results of the German Gynecological Oncology Working Group (Arbeitsgemeinschaft Gynäkologische Onkologie, or AGO) study were also presented, demonstrating the feasibility of a dose-dense biweekly protocol [10]. This trial was designed to compare the frequency of BCS, the response rates, and the safety between two epirubicin- and paclitaxel-containing regimens given either as dose-dense sequential intensified chemotherapy (arm A) or in a standard dose (arm B), both as preoperative therapy for primary breast cancer. Patients with large primary tumors (>3 cm) or inflammatory disease were randomly assigned to receive either three cycles of epirubicin 150 mg/m^2 followed by three cycles of paclitaxel 250 mg/m^2 every 2 weeks with granulocyte colony-stimulating factor support or four cycles of combination epirubicin 90 mg/m^2 and paclitaxel 175 mg/m^2 every 3 weeks as preoperative therapy. A total of 631 patients were enrolled. Preliminary data from 475 patients demonstrated a significantly higher frequency of BCS (66% versus 55%; $P = 0.016$), pCR (18% versus 10%; $P = 0.03$), and negative axillary lymph nodes at surgery (51% versus 42%; $P = 0.098$) with the every-2-week regimen.

The phase III GeparDuo (the second German Preoperative Adriamycin and Docetaxel (GerparDo) trial) (n = 913) of the German Adjuvant Breast Cancer Group (GABG) compared the pathologic locoregional complete response rate achieved with preoperative administration of the 8-week dose-dense combination regimen ADOC (doxorubicin 50 mg/m^2 plus docetaxel 75 mg/m^2 every 14 days for four cycles with filgrastim support), as studied in the predecessor study GeparDo, with that of a 24-week sequential schedule of AC followed by docetaxel (AC-DOC) (doxorubicin 60 mg/m^2 plus cyclophosphamide 600 mg/m^2 every 21 days followed by docetaxel 100 mg/m^2 every 21 days for four cycles each), similar to one of the treatment arms in the NSABP B-27 trial [11].

A pCR was achieved in 94 patients (10.6%), but the likelihood was significantly greater with AC-DOC (14.3%; n = 63) than with the ADOC regime (7.0%; n = 31) (odds ratio 2.22, 90% CI 1.52 to 3.24; $P < 0.001$). Independent predictors of achieving a pCR included the use of sequential therapy, high tumor grade, and negative hormone receptor status. The response rates detected by palpation and by imaging were significantly higher with AC-DOC (85.0% and 78.6%, respectively) than with ADOC (75.2% and 68.6%, respectively; both P values <0.001). The rates of BCS were 63.4% for AC-DOC and 58.1% for ADOC ($P = 0.05$).

Evaluation of early response

As shown in the studies, women with an early or mid-course response to neoadjuvant chemotherapy have chemosensitive

tumors and a high probability for a pCR at surgery. Therefore, assessing early tumor response to chemotherapy is crucial to avoid unnecessary toxicity without potential benefit from the treatment. Neoadjuvant chemotherapy response is currently achieved by monitoring changes in tumor size using clinical examination based on palpable change in tumor size backed up by mammography and/or ultrasound.

Relevant changes (for example, partial remissions, defined as a reduction in the product of the two largest perpendicular diameters of the primary tumor size by 50% or more) in tumor size can be observed at as early as 4 to 6 weeks (that is, two cycles) of chemotherapy. Early detection of response might therefore be used as follows [2]:

- as a predictor of pathologic response
- as a predictor of long-term outcome
- as a decision aid to switch therapy
- to identify patients who might or might not benefit from a switch in therapy.

One approach to use this early information on response in the clinical setting to tailor further treatment strategies for individual patient therapy has been evaluated in the GeparTrio trial, the first prospective randomized study to address patients with tumors that do or do not show an early response [12]. Of 2,090 patients enrolled in the GeparTrio study, 622 (29.8%) who did not respond to two initial cycles of TAC (docetaxel at 75 mg/m^2, doxorubicin at 50 mg/m^2, and cyclophosphamide at 500 mg/m^2) with a decrease in tumor size by at least 50% were randomly assigned to switch to a better tolerated non-cross-resistant regimen consisting of four additional cycles of TAC (n = 321) or to four cycles of vinorelbine at 25 mg/m^2 and capecitabine at 2,000 mg/m^2 (NX) (n = 301).

Sonographic response rates were 50.5% for the TAC arm and 51.2% for the NX arm. The difference of 0.7% (95% CI −7.1% to 8.5%) demonstrated non-inferiority of NX (P = 0.008). Similar numbers of patients in the two arms received BCS (184 [57.3%] in the TAC arm versus 180 [59.8%] in the NX arm) and had a pCR (5.3% versus 6.0%). Fewer patients in the NX arm than in the TAC group had hematological toxic effects, mucositis, infections, and nail changes, but more had hand-foot syndrome and sensory neuropathy. In conclusion, pCRs to both regimens were marginal. Among patients who did not respond to the initial neoadjuvant TAC treatment, similar efficacy but better tolerability was observed by switching to NX than continuing with TAC.

The GeparTrio study also examined the benefit of an intensified neoadjuvant chemotherapy regime consisting of an additional four (n = 704) or six (n = 686) TAC cycles for those women who responded to two initial cycles of TAC (n = 1,390) [13]. Patients receiving a total of eight TAC cycles had statistically significantly higher sonographic response rates, but not pCR rates, than those receiving six TAC cycles. However, eight TAC cycles showed more side effects. Therefore, eight cycles of TAC cannot be recommended for the whole group of patients responding to two initial cycles of TAC.

Predictors of response

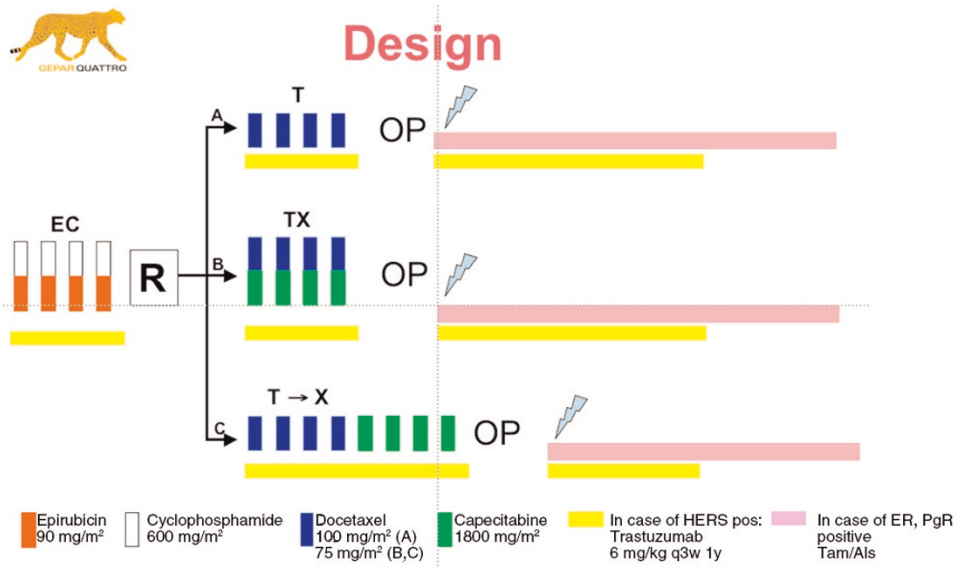
Efforts have been made to identify more accurately the likelihood of pCR under neoadjuvant chemotherapy. The most important predictive marker concerning response to a preoperative taxane-anthracycline-based regimen is negative hormone receptor status. However, despite a pathologic complete remission rate exceeding 40%, survival of patients with this phenotype was reported in several studies to be shorter than for those with receptor-positive tumors [1]. Some studies identified a lower response rate for operable invasive lobular carcinomas. So far, trials with various biological markers like HER2 and topoisomerase IIa have revealed heterogeneous data concerning the prediction of response to specific therapies. Currently, a set of biological markers, rather than a single one, seem to be important to differentiate between a high or low chance for a pCR.

New primary systemic therapy concepts

Patients with no pCR have a significant risk of recurrent disease, and currently no further standard therapy exists. Therefore, alternative regimens are urgently needed to improve therapeutic outcomes for this high-risk population. Ongoing or not-yet-published neoadjuvant trials integrate modern concepts of treatment like tumor targeting with new biological agents or bisphosphonates.

The phase III GeparQuattro study conducted by the AGO and German Breast Group (GBG) study groups is the largest neoadjuvant clinical trial in women with HER2-positive breast cancer. One thousand five hundred and ten women received four cycles of EC (epirubicin 90 mg/m^2 and cyclophosphamide 600 mg/m^2) and were randomly assigned to either four cycles of docetaxel (100 mg/m^2) (arm A) or four cycles of docetaxel (75 mg/m^2) plus capecitabine (1,800 mg/m^2) (arm B) or four cycles of docetaxel (75 mg/m^2) followed by four cycles of capecitabine (1,800 mg/m^2) (arm C) (Figure 1). Women with HER2-positive tumors (n = 456) received trastuzumab 6 (8) mg/kg of body weight every 3 weeks concomitantly with all neoadjuvant chemotherapy before surgery and for up to 1 year after surgery. To minimize the cardiac risk, patients with any previous heart problems and/or an ejection fraction below 55% were excluded. As the analysis of efficacy has shown, the pCR rate (primary endpoint) in women with HER2-positive tumors was significantly increased by the addition of trastuzumab (45.5% versus 19.5%) (Figure 2). The addition of trastuzumab to the

Figure 1



Study design of the GeparQuattro study. EC, epirubicin and cyclophosphamide; ER, estrogen receptor; OP, operation (surgery); PR, partial response; R, random assignment; T, trastuzumab; X, capecitabine. Reprinted with permission [17].

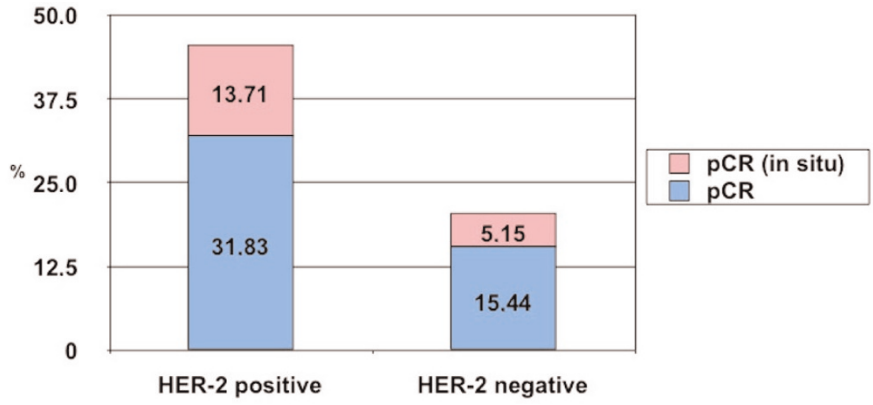
combination of EC and docetaxel and capecitabine is feasible without clinically relevant cardiotoxicity [14] (Figure 3). The addition of capecitabine, neither concomitantly nor in sequence, did not improve the pCR rate.

The multicenter phase II TECHNO (Taxol-Epirubicin-Cyclophosphamide-Herceptin Neoadjuvant) study of the AGO evaluates preoperative 4 × EC 90/600 mg/m^2 every 3 weeks followed by 4 × paclitaxel 175 mg/m^2 every 3 weeks with a trastuzumab loading dose of 8 mg/kg followed by 6 mg/kg every 3 weeks, followed by surgery and postoperative trastuzumab 6 mg/kg every 3 weeks for 9 months in 230 patients with HER2-positive breast cancer (immunohistochemistry 3+ or fluorescence *in situ* hybridization [FISH]-positive confirmed by central pathology) [15]. Radiotherapy and endocrine therapy were applied according to standard recommendations. In 119 analyzed patients, 37% achieved a histopathologic complete response and 17% had only residual ductal carcinoma *in situ* in the breast. Seventy-three percent of women showed histologically negative axillary nodes at surgery. Updated data were scheduled to be available at the end of last year.

The currently recruiting, randomized, open-label multicenter phase III Neo-ALTTO (Neoadjuvant Lapatinib and/or Trastuzumab Treatment Optimisation) study is comparing the efficacy of neoadjuvant lapatinib (a novel orally active small-molecule and dual-tyrosine kinase inhibitor of both epidermal growth factor receptor and HER2) plus paclitaxel, versus trastuzumab plus paclitaxel, versus concomitant lapatinib and trastuzumab plus paclitaxel given as neoadjuvant treatment in HER2-overexpressing and/or amplified primary breast cancer (Figure 4). Patients will be randomly assigned to receive lapatinib 1,500 mg daily, trastuzumab 4 mg/kg intravenous (iv) load followed by 2 mg/kg iv weekly, or the lapatinib 1,000 mg daily with trastuzumab 4 mg/kg iv load followed by 2 mg/kg iv weekly for a total of 6 weeks. After this biological window, patients will continue on the same targeted therapy plus weekly paclitaxel 80 mg/m^2 for a further 12 weeks, up to definitive surgery. After surgery, patients will receive three courses of adjuvant chemotherapy with FEC followed by the same targeted therapy as in the neoadjuvant setting for a further 34 weeks. The planned total duration of the anti-HER2 therapy will be 1 year. The primary objective of this study is to evaluate and compare the rate of pCR at the time of surgery (18 weeks) in patients randomly assigned to receive neoadjuvant lapatinib or trastuzumab or their combination plus paclitaxel. The estimated enrollment will be 450 patients. The study started in November 2007 and will be completed in September 2009.

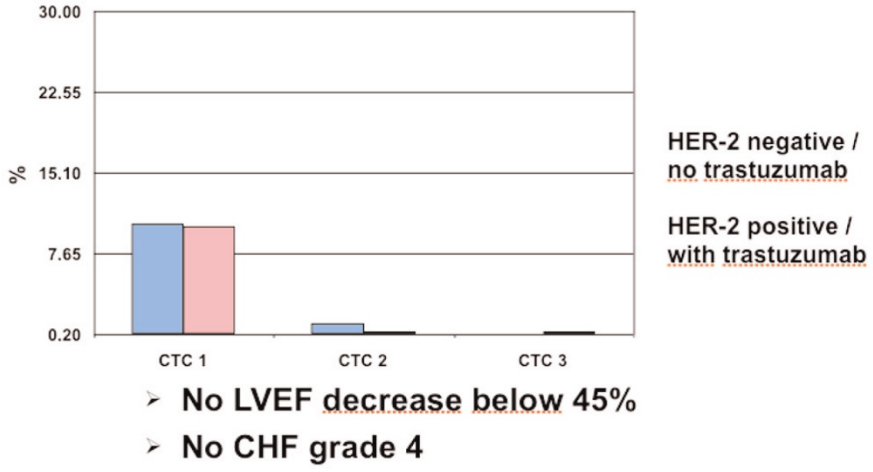
The PREPARE (Preoperative Epirubicin Paclitaxel Aranesp) phase III study was initiated in 2002 and was developed, conducted, and analyzed by the AGO and GBG. It was designed to evaluate the relapse-free survival time and OS of a sequential dose-dense and dose-intensified regimen of epirubicin, paclitaxel, and CMF compared with preoperative sequential administration of epirubicin and cyclophosphamide followed by paclitaxel sequential interval-shortened and dose-intensified preoperative use of epirubicin, paclitaxel, and CMF with preoperative sequential administration of epirubicin and cyclophosphamide followed by paclitaxel in

Figure 2



GeparQuattro study: pathologic complete response (pCR) rates in women with HER2-positive or -negative breast cancer.

Figure 3

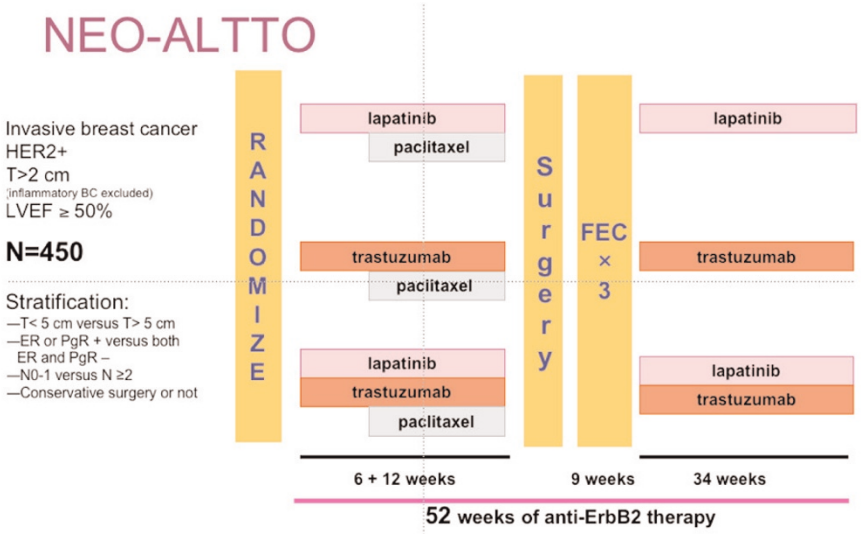


GeparQuattro study: cardiac events in women with HER2-positive and -negative breast cancer. CHF, congestive heart failure; CTC, crackle transmission coefficient; LVEF, left ventricular ejection fraction.

733 women with primary breast cancer. Pegfilgrastim was used as a secondary preventive after febrile neutropenia in the standard arm of the study or, in exceptional cases, after severe febrile neutropenia necessitating the postponement of treatment by more than 1 week. In addition, the influence of darbepoetin alfa on response rate and quality of life was investigated in both treatment arms. An interim analysis showed that the pCR rate was significantly higher in the dose-intensified arm compared with the standard arm (18.7% versus 13.2%; $P = 0.0425$). The use of darbepoetin alfa to support neoadjuvant chemotherapy kept hemoglobin levels stable and had no significant impact on tumor response to chemotherapy at the time of surgery [16]. Long-term follow-up data showed no differences with regard to the comparison of the two chemotherapy regimen. However, there were more relapses and deaths in the group of patients treated with darbepoetin alpha.

The current study of the GBG and AGO groups, GeparQuinto, is addressing three questions with randomizations for separate subgroups: (1) In patients with HER2-negative tumors, we investigate the role of bevacizumab given concomitantly to epirubicin/cyclophosphamide (EC) followed by docetaxel (D) chemotherapy. (2) In patients with HER2-negative tumors not responding to EC with or without bevacizumab, we investigate the role of Everolimus (RAD 001) in combination with paclitaxel. (3) In patients with HER2-positive tumors we compare lapatinib against trastuzumab

Figure 4



Design of the Neoadjuvant Lapatinib and/or Trastuzumab Treatment Optimisation (Neo-ALTTO) study. ER, estrogen receptor; FEC, fluorouracil, epirubicin, and cyclophosphamide; LVEF, left ventricular ejection fraction; PgR, progesterone receptor; T, trastuzumab.

given concomitantly with EC-D. As of March 2009, the trials have recruited 600 out of 2400 patients.

Conclusions

Neoadjuvant chemotherapy for early breast cancer is a major development with important implications for the management of this disease. Originally used only in women with locally advanced inoperable breast cancer, PST can now be offered as a very good option for primary operable disease in patients who are candidates for adjuvant systemic chemotherapy, irrespective of the size of the tumor [1].

The available data suggest a significant and important correlation between pCR after neoadjuvant therapy and DFS as well as OS. Moreover, PST increases the rate of BCSs and is associated with a lower rate of positive axillary lymph nodes at the time of surgery [1]. The preoperative addition of a taxane to preoperative AC results in a significant increase in the rate of cCR, pCR, and negative axillary nodes in patients with operable breast cancer.

At least six cycles of an anthracycline- and taxane-containing regimen should be planned and given preoperatively over the course of 4 to 6 months [1]. Trastuzumab is recommended for patients with HER2-positive tumors. The concurrent use of the anti-HER2 antibody with an anthracycline-containing regimen should be given only in clinical trials. Individualization of neoadjuvant therapy for breast cancer according to mid-course response or to molecular tumor characteristics will be one of the most important goals in the coming years.

This article is part of a review series on *Recent advances in systemic therapy*, edited by Paul Ellis.

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Competing interests

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