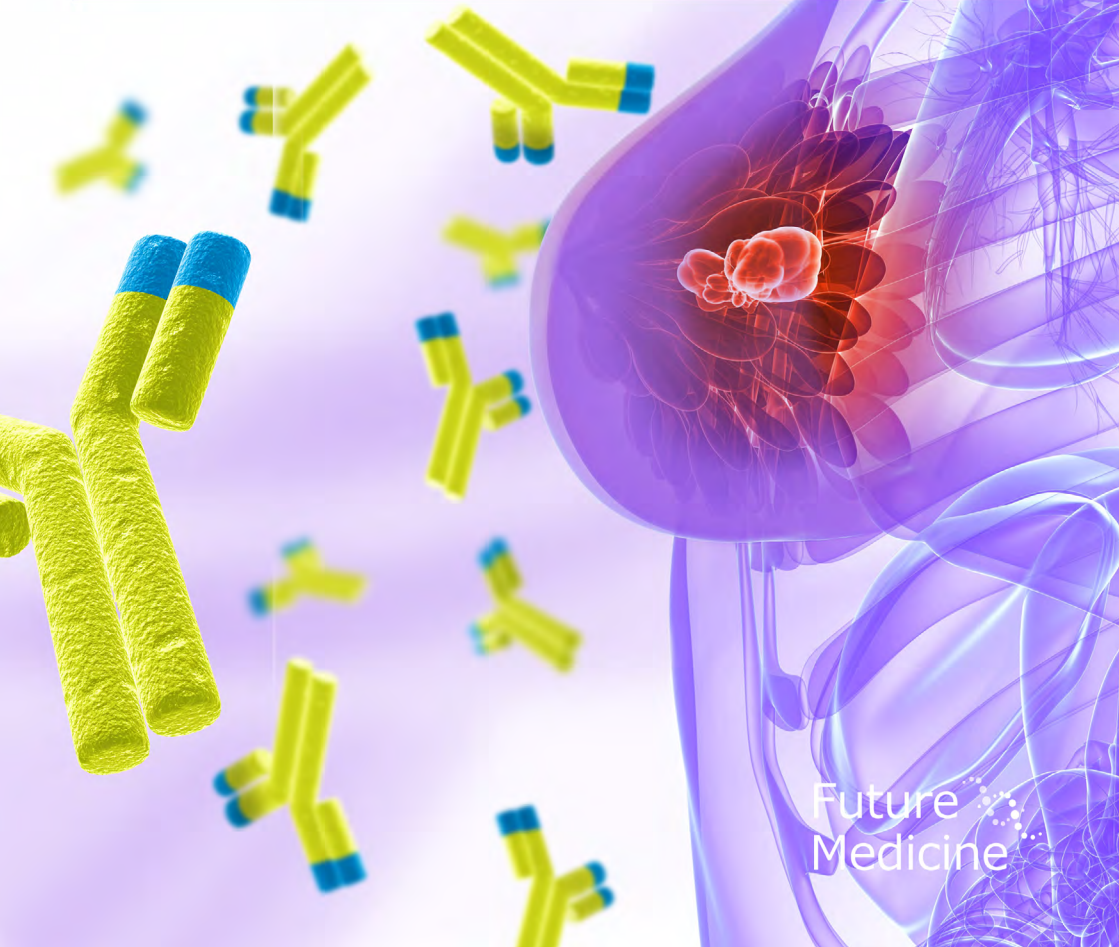
Clinical Insights

Neoadjuvant Therapy in Breast Cancer

Mario Campone and
Jean-Sébastien Frenel



Future Medicine

Clinical Insights: Neoadjuvant Therapy in Breast Cancer

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Clinical Insights

Neoadjuvant Therapy in Breast Cancer

Contents

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Clinical Insights

FOREWORD

Neoadjuvant therapy in breast cancer

Mario Campone & Jean-Sébastien Frenel

Neoadjuvant chemotherapy is the standard of care in patients with locally advanced breast cancer. The objectives of neoadjuvant chemotherapy are to improve breast conservative surgery and to control micrometastases with the hope of improving survival.

The first generation of clinical studies, before the era of taxanes, compared the same chemotherapy regimen delivered in the neoadjuvant setting to the adjuvant setting. Theses trials demonstrated no difference in terms of disease-free survival and overall survival but a significant reduction in the mastectomy rate following neoadjuvant chemotherapy without increase of local recurrence.

The second generation of randomized clinical trial studies comparing different chemotherapy regimens have been designed to improve tumor response. The results of these studies seem to show that the addition of taxanes increase the clinical response rate but without increasing the rate of conservative surgery.

The third generation of clinical studies, the era of targeted therapy including anti-HER2 therapies, included patients with operable breast cancer. The objectives of these studies were to increase the rate of pathologic complete response and survival. The first results with trastuzumab combined with pertuzumab or lapatinib seems to justify this

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therapeutic approach in patients with breast cancer overexpressing HER2.

However, many questions remain regarding the identification of clinical, biological, and pathological factors, which could be used as surrogate markers.

In this book, **Chapter 1** by Beresford reviews and discusses the current options in the neoadjuvant setting. Mailliez *et al.* describe the evaluation of response to treatment and the different pathological classifications in **Chapter 2**. Semiglazov and Semiglazov defines the main goals for neoadjuvant systemic therapy in **Chapter 3**. Brown and Chan provide details about the evolution in neoadjuvant systemic therapy with the development of targeted agents **(Chapter 4)**. Kraay and Lyons defines the radiation recommendations after surgery **(Chapter 5)**. Finally, Frenel and Campone review the current and forthcoming data on the use of monoclonal antibodies as part of neoadjuvant therapy **(Chapter 6)**.

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Clinical Insights

CHAPTER 1

ASK THE EXPERTS

Neoadjuvant therapy: current options

Mark Beresford

1 Is pathologic complete response of tumor following neoadjuvant systemic therapy correlated with improved disease outcomes?

Pathologic complete response (pCR) after neoadjuvant chemotherapy has been shown to predict for long-term survival in several studies. It is an attractive early assessment of response, easily measured and therefore often reported as an outcome in neoadjuvant trials. However, some studies have failed to demonstrate a correlation with survival and this discrepancy has cast doubt on the prognostic implications of a pCR.

Part of this discrepancy might be due to differences in the definition of a pCR – some studies include axillary lymph node response, while others just look at the primary tumor; some allow preinvasive, *in situ* or even focally invasive disease in the pCR category, while others only include eradication of all disease.

We also know that tumor biology is important. While estrogen receptor (ER)-positive luminal A-like tumors have a good prognosis, they tend to have very low pCR rates.

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On the other hand, triple-negative and HER2-positive tumors have poorer prognoses but a higher pCR rate.

The German Breast Group correlated long-term outcome with pCR rates in a review of over 6000 patients treated with neoadjuvant chemotherapy [1]. In the group as a whole, pCR was correlated with improved disease-free survival (hazard ratio of 0.446 if no residual invasive or *in situ* disease). When subdivided by tumor biology, pCR was not predictive of outcomes in luminal A or luminal B HER2-positive tumors. The results with the luminal A group were not surprising given the relative lack of chemotherapy response in these tumors. Even with anti-HER2-directed therapy, pCR was not predictive in the luminal B HER2-positive tumors, but the pCR rates were actually very low in this group, in fitting with observations in the adjuvant trastuzumab trials. However, pCR was a particularly strong predictor of outcome in triple-negative and HER2-positive nonluminal tumors, where pCR was associated with an excellent prognosis. This information should help inform decision-making with regard to which patients are most suitable for neoadjuvant chemotherapy.

2 Do you recommend neoadjuvant endocrine therapy without chemotherapy for postmenopausal patients with strongly hormone receptor-positive breast cancer?

Neoadjuvant endocrine therapy is an attractive alternative to neoadjuvant cytotoxic chemotherapy in patients with ER-positive breast cancer. It is simpler to deliver, better tolerated and ER-positive tumors tend to respond less well to chemotherapy, at least in terms of pCR rates. However, early studies with neoadjuvant tamoxifen revealed disappointing responses, both in terms of the rate and magnitude of response.

The third-generation aromatase inhibitors (AIs) have been compared with tamoxifen in the neoadjuvant setting in the P024 and IMPACT Phase III randomized trials. In P024, 337 patients were randomized to 4 months of letrozole 2.5 mg daily or tamoxifen 20 mg daily [2]. Clinical response at 4 months favored the letrozole arm (55 vs 36%, $p > 0.001$). The secondary end points of radiological response and number of women undergoing breast-conservation surgery also favored the letrozole arm. The IMPACT trial compared 12 weeks of neoadjuvant treatment with anastrozole, tamoxifen or the combination of both drugs in 330 postmenopausal women [3]. Responses by clinical examination or ultrasound were similar in both groups and the breast-conservation rates were 44% for anastrozole, 31% for

tamoxifen and 24% for the combination (nonsignificant differences). There are several possible explanations for the lack of benefit observed in this study when compared with the P024 trial. It was a three-way randomization (so there were fewer patients in each arm), the minimum tumor size was smaller and the required degree of ER expression was lower. The P024 trial stipulated that tumors should be larger than 3 cm, whereas many patients in the IMPACT trial had smaller operable tumors from the outset. Perhaps more importantly, the IMPACT trial patients received anastrozole for 3 months, while the P024 patients received 4 months of primary endocrine therapy.

The optimal length of treatment with neoadjuvant endocrine therapy is unknown. The majority of patients receive treatment for 3–4 months prior to surgery, but it is not uncommon to treat for a longer period of time, particularly in patients with minimal response at the first assessment. There is a need for more research into the optimal duration of neoadjuvant endocrine treatment. In the 1980s and early 1990s, primary tamoxifen studies in elderly women found that the median time to response was 3–4 months, but some patients required over 12 months before achieving the best response. The lack of a definitive marker of response makes it difficult to assess the optimal duration of treatment. Clinical measurements can be imprecise and inaccurate due to poor reproducibility and observer variability, but no other single method of response assessment has been shown to be any better – mammography and ultrasound tend to underestimate response due to residual fibrosis.

The clinical response rates observed with AIs are as good or better than one might expect with chemotherapy in this group of patients, but unfortunately, there are few direct comparison studies to confirm this. There has been only a single published randomized Phase II study that compared response rates of AI versus chemotherapy in the neoadjuvant setting [4]. Postmenopausal patients were randomly assigned to receive neoadjuvant anastrozole or exemestane for 3 months or doxorubicin with paclitaxel (four 3-weekly cycles). Objective clinical responses rates were the same in both groups (64%) and pCR rates were low in both groups at 3% (endocrine) and 6% (chemotherapy). Breast-conservation rates were slightly, but not significantly, higher in the endocrine group (33 vs 24% $p = 0.058$).

The NeoCent trial planned to randomize between neoadjuvant chemotherapy and endocrine therapy (letrozole) in ER-positive breast tumors, but unfortunately was stopped at the feasibility stage due to poor recruitment. Patients were understandably reluctant to be randomized between the treatment arms, and

both patients and clinicians had a bias towards chemotherapy or endocrine therapy depending on patient and tumor characteristics.

In current practice, neoadjuvant endocrine therapy tends to be offered to elderly women with ER-positive tumors that are either inoperable or would require a mastectomy. Traditionally, patients treated in this way were considered unfit for neoadjuvant chemotherapy, although it is increasingly being recognized that other factors should be considered. The degree of ER expression should be taken into account. Patients are more likely to achieve a significant response to primary endocrine therapy if the tumors express very high levels of ER (Allred score: 8 out of 8) [5]. Although patients with lower Allred scores of 6 or 7 showed similar rates of response, the extent of response was lower than those with an Allred score of 8. Median percentage reductions in tumor volume on ultrasound were 48 and 67%, respectively ($p < 0.05$).

In summary, we should consider neoadjuvant endocrine therapy for postmenopausal women with large, strongly ER-positive tumors, particularly luminal A tumors, which are less likely to respond to chemotherapy. In the absence of clinical progression, patients should be treated for a period of at least 4 months to achieve the best response.

3 What is your opinion concerning the role of dual HER2 inhibition in the neoadjuvant setting in patients with HER2-positive breast cancer (trastuzumab plus pertuzumab or trastuzumab plus lapatinib) for improving the disease outcome?

Several studies have shown that neoadjuvant trastuzumab with chemotherapy substantially improves the pCR rates compared with neoadjuvant chemotherapy alone in HER2-positive breast cancer. The studies with the highest reported pCR rates gave the trastuzumab upfront for longer periods of time rather than introducing it in conjunction with taxanes after anthracycline-based chemotherapy.

It is recognized that multiple pathways can contribute to trastuzumab resistance. Lapatinib inhibits EGF receptor and HER2 activity and prevents signaling via truncated forms of the HER2 receptor that might be resistant to trastuzumab, as well as leading to accumulation of HER2 at the cell surface, thereby potentially enhancing the trastuzumab-dependent cellular cytotoxicity. Dual HER2 blockade has been shown to improve progression-free survival in the advanced setting and this

synergistic effect has been studied in the neoadjuvant setting. Various combinations of trastuzumab, lapatinib and chemotherapy have been tested. The majority of these studies showed that lapatinib was inferior to trastuzumab in terms of pCR rates, but the combination of both drugs together improved outcomes. In the NeoALTTO trial that compared trastuzumab with lapatinib with the combination of both (all given in conjunction with weekly paclitaxel for 12 weeks), pCR rates were 28% (trastuzumab), 20% (lapatinib) and 47% (trastuzumab plus lapatinib). Breast-conservation rates, however, were similar in all groups at around 40% [6]. The NSABP B-41 trial looked at similar combinations with a different chemotherapy regimen (adriamycin/cyclophosphamide × 4, followed by 3-weekly paclitaxel × 4) and again found that the combined HER2 therapy improved pCR rates from 47–49 to 60%, although this was not statistically different [7]. Again the breast-conservation rates were similar. Lapatinib does entail additional toxicity, particularly diarrhea, and this was reflected in the observation that less patients completed the full course of treatment in the dual-blockade arm (63 vs 78% in the trastuzumab-alone arm). It is possible that this resulted in the pCR benefit not achieving significance.

Pertuzumab is a monoclonal antibody directed at the dimerization domain of the HER2 receptor, inhibiting signaling between HER2 and HER3 receptors. There is good evidence of synergy with trastuzumab both in the laboratory and in the clinic in metastatic breast cancer, where significantly longer progression-free survival has been observed when added into the gold-standard first-line combination of docetaxel and trastuzumab (18.5 vs 12.4 months, $p < 0.001$) [8]. NeoSphere is a Phase II study with four neoadjuvant arms: docetaxel plus trastuzumab (arm A), docetaxel plus trastuzumab plus pertuzumab (arm B), trastuzumab plus pertuzumab with no chemotherapy (arm C) and docetaxel plus pertuzumab (arm D) [9]. Almost 400 patients were available for analysis and pCR rates were highest in the combination arm B (arm A: 29%, arm B: 45.8%, arm C: 16.8% and arm D: 24%). The improvement in arm B was statistically significant compared with the standard arm A ($p = 0.014$).

Despite the encouraging improvements in pCR rates, it is disappointing to see no benefit in breast-conservation rates and none of these dual-blockade studies have reported on survival or recurrence outcomes. We know from previous neoadjuvant studies that pCR is related to clinical outcomes particularly in HER2-positive/ER-negative tumors (see **Question 1**), so dual-blockade might be a sensible strategy for these patients. Subgroup analysis of the neoadjuvant dual-blockade trials does tend to show less impressive pCR gains in HER2-positive/ER-positive tumors.

The ongoing Phase III dual-blockade adjuvant trials might help inform the role in the neoadjuvant setting.

4 How should one handle breast cancer patients with complete clinical response following neoadjuvant systemic therapy? Is there a need for surgery or for radiotherapy alone?

A commonly asked question is whether surgical intervention is necessary in patients who have a complete clinical response (cCR) to neoadjuvant chemotherapy. This is particularly pertinent in HER2-positive patients where pCR rates of over 50% are being achieved with combined neoadjuvant chemotherapy and anti-HER2-directed therapy. In many of these patients, the risk of relapse is with systemic disease rather than local recurrence, so extensive locoregional surgery may be of limited benefit and simply expose patients to unnecessary morbidity such as pain, lymphedema and wound infections, as well as the psychological impact of potentially disfiguring surgery.

One of the issues of concern is in the assessment of clinical and radiological response and how closely this correlates with pCR. It is recognized that mammography and ultrasound are relatively poor at assessing response to chemotherapy, and, in fact, are no more predictive of pCR than clinical examination [10]. However, MRI scanning might improve the response assessment and there remains concern about being overly aggressive with surgery in patients with no residual disease.

A retrospective review of a database of 453 patients treated with neoadjuvant chemotherapy at the Royal Marsden Hospital identified 136 who had achieved a cCR [11]. A total of 67 patients had surgery as their primary local therapy, whilst 69 had radiotherapy alone. Prognostic characteristics were similar in both groups and there were no differences observed in overall survival for surgery and no surgery, respectively (74 vs 76% at 5 years follow-up and 60 vs 70% at 10 years). There was a trend for more locoregional recurrence in the no surgery group (10% [surgery] vs 21% [no surgery] at 5 years, $p = 0.09$). These 5-year local recurrence rates are similar to those observed in two other published studies of patients treated with radiotherapy alone (~20–30%). Those no surgery patients who also had a complete response on ultrasound had particularly low local recurrence rates at 8%, so the authors suggest that this subgroup might be best suited to avoiding surgery.

A prospective, randomized trial of surgery versus no surgery after cCR would seem reasonable, and there are such studies in development for HER2-positive patients. Perhaps involving ultrasound or contrast-enhanced MRI scanning in these studies to further characterize response would be appropriate. In the meantime, the standard of care remains a primary surgical approach, although some patients might opt to avoid surgery with an understanding that the local recurrence rates might be a little higher.

5 Does preoperative (neoadjuvant) treatment of breast cancer improve breast-conservation rates because of tumor response to therapy?

In the late 1980s and early 1990s, a number of trials were performed to determine whether the use of neoadjuvant therapy would improve the outcome of patients compared with the same chemotherapy given as adjuvant therapy after surgery. All but one of these clinical trials showed that overall survival was equal whether chemotherapy was given before or after surgery. However, a clear benefit was seen with regard to breast-conserving surgery, with downsizing in the preoperative chemotherapy group resulting in fewer mastectomies. Breast-conservation rates ranged from 63 to 90% in the neoadjuvant patients and from 0 to 78% in the adjuvant patients, with most studies showing something in the order of a 10% improvement in conservation rates.

It should be noted that these studies were performed prior to the widespread use of oncoplastic breast surgery so the results may be less applicable to current practice. In addition, the popularity of neoadjuvant chemotherapy has increased and it is often now employed in patients who might either be suitable for breast conservation at the outset or might still require a mastectomy even if they have a cCR due to very large or multifocal disease at presentation. It is difficult to know how the results of trials from 20 years ago would translate into current practice. Recent attempts have been made at predicting response to neoadjuvant chemotherapy and the likelihood of breast conservation using Breast Cancer Index scores from reverse transcriptase PCR assays [12]. These tools might enable better identification of patients who are likely to benefit from neoadjuvant treatment and who might be converted from a mastectomy to a breast-conserving procedure. However, as with many of these types of predictive tests, they can be misleading and give false confidence in decision-making. They are not likely to influence the decision whether or not to undergo neoadjuvant chemotherapy in the near future.

6 What are the current challenges and uncertainties surrounding neoadjuvant chemotherapy?

There remains uncertainty about the optimal timing of sentinel lymph node biopsy (SLNB) in patients treated with neoadjuvant chemotherapy. It is common practice in patients with clinically negative nodes at baseline to perform a SLNB after neoadjuvant chemotherapy. There are many studies regarding SLNB and neoadjuvant chemotherapy, but few have directly compared pre- and post-chemotherapy timings. The SENTINA (SENTinel NeoAdjuvant) multicenter cohort study was one such study designed to evaluate the timing of SLNB procedures [13]. Patients with clinically normal nodes underwent SLNBs before chemotherapy. If the procedure was positive, a further SLNB was performed after chemotherapy. For women with clinically involved nodes at baseline, chemotherapy was commenced and those whose nodes resolved went on to have SLNBs. Only those who remained clinically node-positive went on to have axillary dissection without SLNB. The detection rates of SLNB before chemotherapy were high (99%), but were lower in those who had a SLNB after chemotherapy (60–80%) with significant false-negative rates (as high as 51% in the patients who had both pre- and post-treatment SLNBs). The trial design was complicated and it is difficult to be sure about comparisons between the groups, but it does seem to suggest that SLNB after neoadjuvant chemotherapy might be less reliable than a pretreatment procedure.

Another area of concern is how best to treat patients who fail to respond to neoadjuvant chemotherapy. Most patients will receive a combination of anthracyclines and taxanes in the neoadjuvant setting. If there is still significant residual disease and extensive nodal involvement following the chemotherapy, there is a temptation to offer more treatment in the adjuvant setting. In ER-positive and/or HER2-positive disease, there are options for further systemic treatment, but in triple-negative disease, the standard approach would be just adjuvant radiotherapy for locoregional control. One option would be to offer further platinum-based chemotherapy – there are some small studies that show good responses in triple-negative tumors receiving cisplatin in the neoadjuvant setting. However, there is no evidence to support cisplatin in patients who have already received, and failed to respond to, anthracyclines and taxanes, and this is of course a significant treatment burden.

Financial & competing interests disclosure

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Clinical Insights

CHAPTER 2

Evaluation of complete pathologic response

Audrey Mailliez, Géraldine Lauridant-Philippin & Jacques M Bonneterre

Contents

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Learning points

After reading this chapter you will know:

- Neoadjuvant chemotherapy is indicated in inflammatory or locally advanced breast cancers with aim to allow breast conservation in large operable breast tumors.
- Pathologic complete response is known to have a strong association with disease-free survival and overall survival.
- The definition of pathologic complete response is not standardized.
- Pathologic complete response rates differ according to neoadjuvant chemotherapy protocols and breast cancer subtypes.
- In the future, new prognostic factors (including biology, imaging and nuclear medicine) need to be identified.

Summary

This chapter will first introduce the place of neoadjuvant chemotherapy. The evaluation of response to treatment and the different pathological classifications will then be described. The variability of pathological techniques and the consequences will also be explained. The chapter will end with the author's perspectives and final conclusion.

Neoadjuvant chemotherapy (NAC) is the primary systemic treatment received by nonmetastatic breast cancer patients before surgery [1]. This strategy was initially developed for inflammatory or locally advanced unresectable tumors and is nowadays used for operable large breast tumors to allow breast-conserving surgery [2]. NAC protocols have rapidly been developed since Bonnadonna and Fisher described the micrometastatic disease in preclinical and clinical studies [3,4]. Besides, NAC allows early evaluation of tumor response so that an ineffective chemotherapy could be rapidly stopped and that another treatment could be tested.

Pathologic complete response classifications

The assessment of tumor response provides important prognostic information. Pathologic complete response (pCR) is known to show a strong association with disease-free survival and overall survival. However, no definition of pCR is standardized.

At least eight different pathological classifications have been described [5]. The criteria of evaluation are quite different [6]. Some opposed absence of invasion versus persistence of invasive lesions [7–9]. In some of these classifications, the intraductal component is individualized [10,11]. The response can be graded according to the percentage of tumor volume reduction [5,12] or to the size of invasive residual lesion [13]. Few classifications take into account the lymph node's response [9,11,12].

Chevallier *et al.* described four grades of pathological response [10]. In the first, there no any tumor cells and no axillary metastasis. In the second, *in situ* carcinoma is present in the breast. In the third, there are residual invasive tumor cells with fibrosis or sclerosis. In the fourth, little or absence of therapeutics effects can be noted.

Sataloff's classification includes the response in the breast (T) and in the nodes (N) [12]. In the breast, total or almost total therapeutic effects is called Ta, therapeutic effect more than 50% but not total is called Tb, therapeutic effect less than 50% is called Tc and no therapeutic effect is called Td. In the axillary lymph nodes, Na shows evidence of therapeutic effects without residual disease, Nb shows no therapeutic effect nor metastasis, Nc shows therapeutic

Primary systemic treatment: the first treatment received before surgery.

Pathologic complete response: disappearance of the initial tumor described by the pathologist after primary systemic treatment.

effect but persistence of axillary metastasis, and Nd shows axillary metastasis without therapeutic effect.

The National Surgical Adjuvant Breast and Bowel Project (NSABP) classification is much simpler. It distinguishes pCR (no histological evidence of invasive tumor) and presence of invasive disease.

The classification by Sinn *et al.* grades the tumor sclerosis, the residual tumor, the persistence and the size of noninvasive residual tumor in five grades [13].

Honkoop *et al.* takes into account macroscopic and microscopic tumor cells in the breast and in the axillary nodes separated into four grades [7].

Miller and Payne look after response in the breast and in the nodes [9]. There are four groups according the absent, minor, moderate or marked effect on the breast. The fifth group includes the stromal alterations, the *in situ* carcinoma and the absence of tumor cells. The nodes can be negatives, positives with or without therapeutics effects or initially positives but converted to negative after primary systemic treatment.

The Japanese Breast Cancer Society considered the response as absent, slight (divided into mild or moderate), marked or complete according to the percentage of volume reduction from no change to disappearance of tumor cells [5].

In 2003, an international consensus panel's classification described a pCR of invasive tumor if only *in situ* lesions persist and a pCR if any neither invasive nor *in situ* cells are present [11].

We can see that the criteria of pathological response are heterogeneous. These classifications have not been compared in the same study. It is then very difficult to determine if one is better than the others and why. Apart from the real complete response (any invasive or *in situ* tumor cells) or progressive disease, no consensus can be found between these eight classifications.

Pathological techniques for pCR assessment

Moreover, the pathological techniques and the limits of the classifications are responsible for major difficulties in accurate pathological results. The pretreatment sample, and clinical and radiological data are not always available. The evaluation of mastectomy specimens is rarely exhaustive. The pathological evaluation of the response to NAC and its reproducibility between different pathologists are also linked to the techniques, which, in the absence of clear recommendations, vary. There is rarely a total inclusion of the specimen and the number of samples varies between teams. In some studies, 30 [14] and even 50 [15] breast sections are examined, while six

and more sections including one from the nipple are proposed by Chevallier *et al.* [10]. In the study by Sataloff *et al.*, 'multiples' sections from the biopsy site and random sections of the nipple and four quadrants were analyzed [12]. The Miller–Payne scoring system recommends at least four sections in case of macroscopic residual tumor or a sampling of the whole face of the tumor scar [9]. The Residual Cancer Burden is another grading system [16]. It takes into account tumor bed volume, average tumor cellularity, number of involved lymph nodes and the size of the largest metastasis.

The presence of a clip even if a mastectomy is indicated is extremely useful for the pathologist in order to make the sampling more efficient [17].

In all cases, a pCR can be confirmed only if the bed tumor site is histologically identified.

pCR according NAC protocols & breast cancer subtypes

pCR rates differ according to NAC protocols and breast cancer subtypes. Besides, low pCR rates are shown in estrogen receptor-positive low proliferation tumors because of a too precocious reassessment after chemotherapy, while response to endocrine therapy occurs often more slowly.

In the NSABP B-18 study [18] that evaluated anthracylins, the pCR rate was 13%. NSABP B-27 [7] and the ECTO I (anthracylin plus taxanes) [19] show a pCR of 18.9 and 23%, respectively.

Study of increase dose intensity allows increase of pCR, but these results do not translate into statistically significant survival benefits [20].

Targeted therapies improve pCR rates. The first study was NOAH trial, which compared NAC plus trastuzumab followed by surgery and adjuvant trastuzumab to NAC alone followed by surgery in locally advanced or inflammatory HER2-positive breast cancers [21]. The pCR (breast and axillary nodes) rate was increased in the group NAC plus trastuzumab versus NAC alone (38 vs 16%). The benefits of neoadjuvant trastuzumab has been confirmed.

The next section will discuss the double blockage of HER2 protein. Combination of anti-HER2 therapies show benefits first in the metastatic setting [22,23] and has secondarily be used in neoadjuvant breast cancer.

The synergy of trastuzumab and lapatinib was tested in the NeoALTTO trial [24]. Lapatinib is an oral tyrosine kinase inhibitor targeting EGF receptor and HER2. This Phase III trial compared three groups of HER2-positive breast cancer patients with tumors larger than 2 cm

receiving chemotherapy with paclitaxel combined with trastuzumab, lapatinib or both. The rate of pCR evaluated according to the criteria of the NSABP (defined as the absence of invasive residual tumor in the surgical specimen) was higher in the combination arm: 51.3 versus 29.5% in the trastuzumab group versus only 24.7% in the lapatinib-alone group alone.

Another strategy of double anti-HER2 therapy involves pertuzumab. In the NEOSPHERE trial Gianni *et al.*compared four treatment groups in 417 HER2-positive breast cancers patients [25]: one group treated with docetaxel and trastuzumab, a second group with docetaxel and pertuzumab, a third group with docetaxel, pertuzumab and trastuzumab, and the last group by trastuzumab and pertuzumab without chemotherapy. The best rate of pCR was obtained in the pertuzumab + trastuzumab + docetaxel group (45.8 versus 29% in the docetaxel and trastuzumab arm, respectively, 24% with docetaxel and pertuzumab, and 16.8% in the group with targeted therapy alone).

Antiangiogenic therapies have also been evaluated in clinical studies. The efficacy of bevacizumab was evaluated in inflammatory breast cancer in the two French Beverly trials (Beverly 1 in HER2-negative breast cancers [26] and Beverly 2 in HER2-positive breast cancers [27]). These Phase II studies show a particularly high pCR rate (27 and 63.5%, respectively). Data on survival are not yet available. Another Phase II study was performed in operable or locally advanced breast cancers and confirmed high pCR [28].

Triple-negative and inflammatory breast cancers show the highest pCR rates but they have a particularly pejorative outcome, while pCR is rarer with luminal A breast cancer. This subtype of breast cancer is of best prognostic.

Efficacy of treatment translates into response even in absence of pCR, particularly in subtypes where pCR is rare [17]. However, pathologists do not always comment on the presence of chemotherapy effect and the prognostic impact of such data remains limited. Some patients with pCR relapse after NAC. By contrast, others who have only very partial response do not relapse. It is thus interesting to note that gains in terms of pCR rate achieved by optimizing the neoadjuvant protocols (addition of targeted therapies: i.e., trastuzumab in the NOAH trial) do not translate in improvement of overall survival.

Recently, Cortazar *et al.* conducted a large meta-analysis on 12 early randomized NAC trials. Improved outcomes in patients with pCR were demonstrated but any correlation between improvement in disease-free survival and overall survival and increased pCR rates can be made [29].

Pathological assessment: evaluation of the surgical specimen by the pathologist according to different techniques.

In the future, new prognostic factors could be identified. The study of early response to chemotherapy through different techniques of biology, imaging or nuclear medicine will allow ineffective treatments to be stopped and protocols can then be individualized. Kolesnikov-Gauthier *et al.* demonstrated a significant relationship between early isotopic response (assessed after a single cycle of chemotherapy), clinical response evaluated according to WHO criteria after three cycles and pCR evaluated after six cycles. Relapse-free survival at 4 years was significantly longer in responders (defined by a decrease in standardized uptake value of at least 15% after the first course of chemotherapy) than in nonresponders: 85 versus 44% (p = 0.01) [30].

Pathological assessment of the response is undoubtedly improved by an increase of our knowledge of tumor biology. New agents are now tested in a neoadjuvant setting to give earlier information on efficacy and safety, compared with adjuvant studies in which laboratories have to look for results for a long time. Pathologic response is an important element of neoadjuvant breast cancer therapy; however, the evaluation is very difficult and at least partly subjective that its use as a prognostic factor is questioned. Gradually, other elements such as biology, imaging and nuclear medicine deputize these pathological findings.

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Multiple choice questions

1. Concerning neoadjuvant chemotherapy, which of the following is true?
   - a. Neoadjuvant chemotherapy (NAC) is indicated in inflammatory breast cancers
   - b. NAC does not allow breast cancer conservation
   - c. NAC is never proposed in operable breast cancers
   - d. Surgery is needed after clinical complete response to NAC
2. Regarding pathological response, which of the following is true?
   - a. The definition of pathologic complete response (pCR) is clearly standardized
   - b. pCR is known to show a strong association with disease-free survival and overall survival
   - c. Chevallier's classification is the one that is used
   - d. Assessment of pathological response never takes into account the node's response
3. One of the statements regarding pathological techniques is false, which is it?
   - a. The number of samples from a mastectomy specimen varies from teams
   - b. A pCR can be confirmed only if the bed tumor site is histologically identified
   - c. A full inclusion of the mastectomy specimen is always made
   - d. The presence of a clip is useful for the pathologist in order to make the sampling more efficient
4. Which of these sentences concerning the pathological response is not true?
   - a. Triple-negative breast cancers have low pCR rates
   - b. Inflammatory breast cancers show high pCR rates
   - c. pCR is rarer with luminal A breast cancer
   - d. pCR rates differ according to breast cancer subtypes

5. Concerning the effect of systemic treatment on pCR, we can say that which of the following is true:
   a. Antiangiogenic therapies are commonly used in a neoadjuvant setting
   b. Increase dose intensity does not increase pCR
   c. Use of targeted therapies in a neoadjuvant setting improves pCR rates
   d. Adjunction of taxanes does not modifiy pCR

Clinical Insights

CHAPTER 3

Recommendation and predictors of pathologic response

Vladimir F Semiglazov & Vladislav V Semiglazov

Contents

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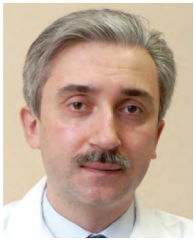
Vladislav V Semiglazov



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Learning points

After reading this chapter you will know:

- Advances in the understanding of breast cancer biology heterogeneity has led to the use of different types of neoadjuvant systemic treatment: neoadjuvant chemotherapy, neoadjuvant endocrine therapy and neoadjuvant target therapy (in HER2-positive breast cancer).
- Pathologic complete response after neoadjuvant systemic treatment is defined as complete absence of either invasive or non-invasive breast cancer, both in the breast and in the axillar lymph nodes and can determine individual prognosis and best determine patients with favorable prognosis.
- In patients with clinical complete response upon completion of neoadjuvant therapy, radiotherapy alone is a treatment modality that is capable of providing survival outcomes as good as those seen in patients where surgery was performed.
- A prospective randomized trial addressing the need for surgery after clinical complete response would seem reasonable in patients with magnetic resonance or positron emission tomography-defined complete remissions.

Summary

Three main goals for neoadjuvant systemic therapy in breast cancer were defined: to reduce mortality from breast cancer, to improve surgical options, and to acquire early information on response and biology of the disease. Advances in knowledge of breast cancer biology heterogeneity has led to the use of different types of neoadjuvant systemic therapy: neoadjuvant chemotherapy, neoadjuvant endocrine therapy and neoadjuvant target therapy (in HER2-positive breast cancer).

Neoadjuvant computed tomography

Neoadjuvant therapy is recommended not only for locally advanced (LA) and inflammatory breast cancer (BC) but also as an option for primary operable disease without compromising the long-term outcome [1,2].

Neoadjuvant chemotherapy (CT) is not associated with an increase in survival rates, although the results of the multiple studies designed to assess the advantages of the neoadjuvant CT in operable BC show that breast conserving treatment rates can be increased with this approach [3]. As mentioned before, the key goal of neoadjuvant treatment is to achieve tumor downstage in order to perform surgery, because even today many patients present with LABC at the time of diagnosis. In the case of a multicentric or CT-resistant tumor, mastectomy should be considered as the only acceptable option. Currently, there are no known contraindications to perform breast reconstructive surgeries in such cases [4]. Early information on treatment response obtained from clinical observation and pathological assessment can be a valuable addition in predicting disease recurrence, survival and even selecting effective regimens for adjuvant use.

Neoadjuvant CT with anthracycline and/or taxane-containing regimens in elderly patients with estrogen receptor (ER)- and/or progesterone receptor (PR)-positive tumors is less effective.

Preoperative CT is more effective in patients with ER- and PR-negative tumors. The highest rates of response were observed in patients with hormone receptor (HR) negative and/or HER2neu positive tumors with high proliferative activity compared with patients whose tumors were HR-positive [5]. In the ECTO I trial, the rates of pathologic complete response (pCR) after neoadjuvant CT were significantly higher in women with ER-negative tumors (42 vs 12% in patients with ER-positive tumors) [6]. In the NSABP B-27 study, ER-negative tumors had significantly higher rates of pCR after treatment both with doxorubicin + cyclophosphamide or with consecutive

Tumor downstaging: reduction in T stage of at least one category (e.g., T4 to T3/T2; T3 to T2). Similarly, nodal downstaging is a reduction in N-stage category.

Pathologic complete response: after neoadjuvant systemic treatment defined as complete absence of either invasive or noninvasive breast cancer both in the breast and in the axillar lymph nodes.

doxorubicin + cyclophosphamide + docetaxel for four cycles compared with ER-positive tumors [7].

Definition & impact of pCR on prognosis after neoadjuvant therapy

pCR can be used as a main criteria in evaluating neoadjuvant CT effectiveness and as a predictor of long-term outcomes. At the very same time, there is no common understanding of the term. In some trials, axillar lymph node status was not taken into consideration, while others evaluated both the tumor and the lymph node downstage and status after resection.

Absence of a common definition for pCR is a complicated issue that requires standardization. In some studies, presence of ductal carcinoma *in situ* (DCIS) or even multiple microscopic foci of invasive cancer were considered pCR, in others, only complete absence of tumor tissue, either invasive or noninvasive cancer was considered a pCR.

Over a long time, the subpopulations of patients with minor residual disease, such as residual DCIS, foci of invasive cancer less than 5 mm in the largest dimension, or no residual tumor in the breast but nodal involvement, have often been considered to have achieved pCR. However, according to von Minckwitz *et al.*, residual cancer burden can be associated with an increased risk of relapse and death compared with 'true' complete responders; for example, pathological measure of complete regression (response) of primary tumor after neoadjuvant systemic treatment and pathological measure of complete regression (response) of metastatic axillary lymph nodes after neoadjuvant systemic treatment [8]. These patients have the lowest HR for disease-free survival (DFS) and overall survival (OS) compared with patients with any residual disease. It is notable that Schott and Hayes have shown that in the subgroups of patients with slowly proliferating HR-positive tumors, pCR is not associated with better prognosis [9], whereas in patients with high proliferating tumors, pCR can be used to determine prognosis rather accurately. Currently, the definition of pCR proposed by the St Gallen panel is being used widely. It recognizes the aforementioned subgroups. After risk adjustment to this particular definition of pCR, it became clear that the prognostic impact of the complete response is highest in triple-negative and HER2-positive tumors. Patients of these subtypes when pCR is achieved tend to have a prognosis similar to that of patients with luminal A tumors.

Intrinsic subtypes of BC differ in incidence of pCR. Prognostic impact of pCR is also different. Luminal tumors have a low rate of pCR, but the overall prognosis for this subtype is generally

favorable. Patients with triple-negative tumors have a relatively high rate of pCR but generally unfavorable outcome [8]. pCR defined as the complete eradiction of the tumor with no residual disease, either invasive or noninvasive, with no tumor tissue found in the nodes can be used to highlight patients with more favorable outcome. Patients with residual disease should not be considered complete responders. pCR rate is a suitable end point in evaluating the efficacy of neoadjuvant CT in tumors with high proliferative activity; for example, for HER2-positive and triple-negative tumors but not for luminal A tumors.

Neoadjuvant endocrine therapy

The duration of neoadjuvant hormonal treatment for BC in most studies was 3–6 months. The few studies that investigated prolonged treatment with neoadjuvant endocrine therapy suggest that a further reduction in tumor size can be achieved and that even surgery can be withheld for elderly women on continuing hormonal treatment.

For many years, neoadjuvant CT has been the mainstay of the primary approach, but more recently neoadjuvant endocrine therapy has emerged as an attractive alternative in postmenopausal women with large HR-positive BCs. A number of randomized trials (e.g., P024, IMPACT, PROACT) have compared various aromatase inhibitors directly with tamoxifen. An important endpoint in each of these studies has been the rate at which breast conservation has been achieved. The presence of steroid HRs (ER and/or PR) are a target for endocrine therapy [10–14].

Before the authors' trial, there were few, if any, direct comparisons of neoadjuvant hormone and CT in postmenopausal patients with HR-positive BC [15,16].

The authors have conducted an open-label, randomized Phase II trial of once-daily endocrine therapy (exemestane or anastrozole) versus CT (doxorubicin and paclitaxel, four 3-week cycles) in postmenopausal women with primary ER-positive BC. A total of 239 patients with ER-positive and/or PR-positive BC (T2N1-2, T3N0-1 and T4N0M0) enrolled in the study. Patients were randomized to receive neoadjuvant CT (doxorubicin 60 mg/m^2 with paclitaxel 200 mg/m^2, four 3-week cycles, 118 patients or neoadjuvant endocrine therapy anastrazole endocrine treatment 1 mg/day or exemestane 25 mg/day for 3 months, 121 patients).

All patients were considered to be ineligible for breast-conserving surgery at enrollment. After breast-conserving surgery all patients received radiotherapy (50 Gy in 25 fractions). The median follow-up time was 5.6 years.

The primary efficacy end point was already reported [15]. Overall response

(OR = CR + PR) was similar in the endocrine therapy group (65.5%) compared with the CT group (63.6%; p >0.5). Similar OS rates were observed in patients who were receiving exemestane and anastrozole. It allowed us to unite the data on all patients who were undergoing endocrine therapy into one endocrine therapy group. There was a notable trend toward higher ORR among patients with high levels of ER (Allred score ≥6) in the endocrine treatment group compared with the CT group (43 vs 24%, p = 0.054). pCR occurred in 6 and 3% of patients receiving CT and endocrine therapy, respectively (p > 0.05).

Preoperative endocrine therapy with aromatase inhibitors is a reasonable alternative to preoperative CT for postmenopausal women with ER-positive BC.

According to the St Gallen recommendation, neoadjuvant endocrine therapy should be considered a treatment option for the management of postmenopausal patients with a high expression of HRs in the tumor [17]. The duration of such treatment should last for 5–8 months, or until maximum tumor response is achieved.

Neoadjuvant therapy in HER2-positive BC

Trastuzumab, pertuzumab and lapatinib target different epitopes of HER2, and HER1 improves results of neoadjuvant CT in patients with HER2-positive LABC.

Amplification or overexpression of HER2 is a known factor of progression of breast cancer. It is associated with aggressive disease, with a specific pattern of metastatic spread and poor outcome [18]. It is present in approximately 22% of early BCs, 35% of locally advanced and metastatic tumors, and 40% of inflammatory BCs. Patients presenting with inoperable disease at the time of diagnosis are in particular need of effective treatment that is capable of providing downstage. Trastuzumab (Herceptin®, Roche, Basel, Switzerland), a recombinant humanized monoclonal antibody that targets HER2, is moderately effective as monotherapy with response rates ranging from 13 to 34% [19]. It is also capable of increasing response rates when used in combination with CT in HER2-positive metastatic and even OS in early operable BC [20–23].

Neoadjuvant CT with trastuzumab followed by adjuvant trastuzumab versus neoadjuvant CT alone in patients with HER2-positive LA or inflammatory BC was studied in the NOAH study. 228 patients with centrally confirmed HER2neu-positive LABC were randomized to a CT regimen – four cycles of paclitaxel; three cycles of doxorubicin plus paclitaxel; and three cycles of cyclophosphamide, methotrexate and fluorouracil,

with and without trastuzumab. The addition of trastuzumab significantly improved OR and pCR rates (43 vs 23%, p = 0.002) [18].

Despite the current precautious mainstay, the trial showed that concurrent administration with doxorubicin is an option. Only two such patients (2%) developed symptomatic cardiac failure. Trastuzumab significantly improved all treatment results and trastuzumab-containing regimens superseded all end points in all subgroups tested, including patients with inflammatory BC, who benefited substantially [19,24]. The addition of trastuzmab significantly improved event-free survival, almost doubled rates of pCR, reduced risks of relapse and BC-related death.

However, in some patients disease progression still occurs. Pertuzumab and trastuzumab target different epitopes of HER2, and their use in combination has demonstrated improvement in response rates. The NEOSPHERE study assessed the efficacy and safety of pertuzumab added to trastuzumab-based neoadjuvant CT in women with HER2-positive operable, LA/inflammatory BC who had not received prior cancer therapy [25].

Approximately 40% of patients had LA/inflammatory BC and approximately 50% were ER/PR negative. THP combination (docetaxel + trastuzumab + pertuzumab) significantly improved the pCR rate compared with docetaxel + trastuzumab alone (45.8% [95% CI: 36.1–55.7] vs 29.0% [95% CI: 20.6–38.5]; p = 0.0141). Patients receiving THP had the highest pCR rate regardless of ER/PR status, although the greatest treatment benefit in all four arms was observed in ER/PR-negative patients. The CT-free trastuzumab + pertuzumab arm achieved a pCR rate of 16.8%. THP had a similar safety profile to docetaxel + trastuzumab. The incidence of adverse events was lowest in the trastuzumab + pertuzumab arm.

Dual HER2 inhibition is being examined in neoadjuvant and adjuvant settings. The NeoALTTO study showed clear benefits of dual inhibition used in the neoadjuvant setting. Simultaneous use of lapatinib and trastuzumab in the neoadjuvant setting resulted in higher pCR rates than either of the therapies alone (51.3% for combined therapy vs 29.5% for trastuzumab vs 24.7% for lapatinib monotherapy, respectively; p < 0.01). Objective clinical response rates after 6 weeks of combined anti-HER2 therapy alone were comparable with those after 18 weeks of neoadjuvant anti-HER2 therapy plus CT (67.1, 30.2 and 52.6%, vs 80.3, 70.5 and 74.0%, respectively), suggesting that the combination is beneficial in the neoadjuvant setting [26–28].

Surgical management of patients who achieve a complete clinical response after neoadjuvant therapy

Neoadjuvant systemic treatment (NST) is the standard treatment for LABC and a standard option for primary operable disease. The aim of this analysis is to determine, whether radiotherapy after achieving a complete clinical response (cCR) can be considered an option.

We identified eight studies of NST where BC patients who achieved a cCR were eligible for different types of local management: radiotherapy only or surgery. Primary outcomes were loco-regional recurrence, distant DFS and OS [11,29–31].

The authors performed subgroup meta-analyses for the primary outcomes on the basis of local management. Heterogeneity between the risk ratios (RRs) for the same outcome between different studies was assessed by use of the χ^2-based Q statistic.

Rates of pCR range from 25 to 35.8% of patients who had a cCR. If a cCR is considered as a 'test' of pCR then the positive predictive value of cCR in all eligible trials was low (range from 29.9 to 35%). For surgery and no surgery (radiotherapy alone) groups, respectively, there were no significant differences in distant DFS (summary RR: 0.94; 95% CI: 0.91–1.07) or OS (RR: 1.00; 95% CI: 0.99–1.12). But there was trend towards increased locoregional recurrences for the radiotherapy only group (difference in favor to surgery range from 11 to 20%; RR: 1.53, 95% CI: 1.11–2.10; p = 0.02).

In patients with cCR upon completion of neoadjuvant therapy radiotherapy alone is a treatment modality capable of providing survival outcomes as good as in patients with surgery performed. A prospective randomized trial to define the need for surgery after MRI or positron emission tomography-defined cCR is reasonable.

Conclusion

The neoadjuvant (preoperative, primary) use of systemic therapies – chemo- hormone- and targeted-therapies effectively downstages the disease by reducing tumor mass in the breast and the axilla, often making the disease operable without compromising the survival.

Complete clinical response: disappearance of all signs of cancer in response to treatment after clinical evaluation according to Response Evaluation Criteria In Solid Tumors.

The risk of local recurrence is determined by the clinical stage at the time of treatment initiation, intrinsic subtype and pathologic stage after surgery. pCR after NST is defined as complete absence of either invasive or noninvasive BC both in the breast and in the axillar lymph nodes can determine individual prognosis and best determine patients with favorable prognosis. The incidence and prognostic impact of pCR vary among BC-intrinsic subtypes; pCR after NST is a suitable surrogate and point for patients with HER2-positive and triple-negative BC but not for those with luminal A (ER-positive, PR-positive) tumors.

According to St Gallen recommendations, neoadjuvant endocrine therapy can be considered a treatment option for management of postmenopausal patients with high expression of steroid HRs [17].

Amplification or overexpression of HER2 is associated with aggressive disease and poor prognosis of BC.

Trastuzumab, pertuzumab and lapatinib target different epitopes of HER2, and HER1 improves results of neoadjuvant CT in patients with HER2-positive LABC.

A prospective, randomized trial addressing the need for surgery after cCR would seem reasonable in patients with magnetic resonance or positron emission tomography-defined complete remissions.

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Multiple choice questions

1. Which of the following is the goal of neoadjuvant systemic therapy?
   - a. To improve surgical options
   - b. To acquire early information on response and biology of the disease
   - c. To use the most potent agents at the time when most tumor cells are replicating
   - d. To improve patient general status
2. Neoadjuvant chemotherapy is more effective...
   - a. In patients presenting with large tumors at the time of diagnosis
   - b. In elderly postmenopausal patients with estrogen receptor-positive tumors
   - c. In patients with hormone receptor-negative tumors with high proliferation rate
   - d. In patients with family history of breast cancer
3. Which of the following pathology results after surgery is associated with best overall survival results?
   - a. Only residual ductal carcinoma *in situ* in the breast tissue, but no lymph nodes involved
   - b. Microscopic foci of invasive breast cancer in the breast tissue
   - c. Complete absence of invasive and noninvasive cancer, both in the breast and in the lymph nodes studied after surgery
   - d. Complete absence of invasive and noninvasive cancer in the breast, single micro metastasis in one of the lymph nodes after surgery

4. The addition of the drugs targeting HER2-pathway to the neoadjuvant chemotherapy scheme in HER2-positive patients improves
   a. Pathologic complete response rate
   b. Event-free survival
   c. Overall survival rate
   d. Toxicity profile
5. What factors determine the risk of local recurrence after completion of neoadjuvant chemotherapy and surgery?
   a. Initial stage
   b. Intrinsic subtype
   c. Family history
   d. Patient age

CHAPTER 4

Combination chemotherapy and targeted agents

Victoria Brown & Stephen Chan

Contents

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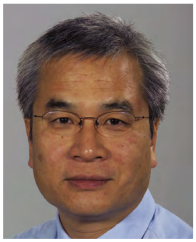
About the authors

Victoria Brown

Victoria Brown trained at Leicester University Medical School (UK), qualifying in 1998. During her oncology training at Leicester University Hospitals, she was awarded a MSc oncology (Honors) and PhD in the Department of Cancer Biomarkers and Prevention. She was appointed consultant in medical oncology at Nottingham University Hospital (UK) in 2012. Her main interest is the in the management of breast and hepatobiliary cancers.

Stephen Chan



Stephen Chan qualified at Nottingham University Medical School (UK). He started his training in oncology at Oxford (UK) and was a Research Fellow at the Ludwig Institute at Cambridge MRC and Imperial College London (UK). He returned to Nottingham after working at the Christie Hospital Manchester (UK). He took up his current post in 1989. Between 1995 and 2000, he chaired the Mid Trent postgraduate educational board. He is a member of national and international research groups including American Society of Clinical Oncology, European Organisation for Research and Treatment of Cancer (Gynae group) and the British Breast Group and was made a Visiting Professor at Nottingham Trent University (UK) in 2011. He is the author of over 80 peer-reviewed scientific papers and principal author of studies in the development of new treatments, including docetaxel and targeting therapy. His current research interests include predictor markers as well as specific antigens in breast and ovarian cancers. He is a member of numerous national and international steering committees for clinical trials. He is currently Director of Clinical Trials in Breast and Gynaecological Research at Nottingham University Hospitals where he works closely with his radiology, pathology and surgical colleagues.

Learning points

After reading this chapter you will know:

- Neoadjuvant chemotherapy is becoming more common practice, allowing inoperable breast tumors to become operable and enabling women with early-stage breast cancer to undergo breast conservation surgery.
- Using the window of opportunity between diagnosis and surgical resection presents additional potential for *in vivo* testing of anticancer agents.
- Achieving pathologic complete response (pCR) after neoadjuvant chemotherapy is associated with better outcomes, highlighting the need for novel therapeutics that will improve pCR rates and clinical outcomes.
- Trastuzumab alongside chemotherapy has become standard for Her2-positive disease and has significantly changed the prognosis for this group of breast cancers.
- There is a growing interest in overcoming resistance to trastuzumab with the development of Her2-targeting agents, such as trastuzumab emtansine and dual blockade (trastuzumab with either pertuzumab or lapatinib).
- Triple-negative breast cancer has higher rates of pCR than other breast tumor types. However, more than half do not achieve a pCR and have a poor prognosis. The lack of drug targetable receptors on these tumors has made improving the available interventions an area of medical need.
- Estrogen receptor-positive cancers represent a heterogeneous group. Neoadjuvant endocrine therapy is currently used as treatment for locally advanced breast cancer in the elderly and frail where chemotherapy is not advised. It could also be considered in place of cytotoxic therapy for postmenopausal patients with tumors with low proliferation rate and high estrogen-receptor expression.

Summary

Neoadjuvant (preoperative/primary) chemotherapy integrated into a multimodality program is the established treatment in locally advanced breast cancer for improving rates of operability and clearance of the primary tumor. The use of neoadjuvant chemotherapy has recently been extended to women who have early-stage breast cancer to improve their options for breast conservation surgery who would otherwise require a mastectomy. Neoadjuvant chemotherapy has shown equivalence in outcomes compared with similar therapy after surgery [1]. However, the neoadjuvant approach offers additional advantages in providing early information on tumor biology and assessment of response or resistance to both standard therapies and novel agents. Biomarkers are being investigated as methods for identifying patients who will most likely benefit from neoadjuvant therapy. The management of breast cancer could be modified based on molecular biology and an approach tailored to each patient. This chapter is intended to give details about evolution in neoadjuvant systemic therapy with the development of targeted agents focusing on: patient selection, to identify patients suitable for neoadjuvant systemic therapy; tumor biology, identifying tumors likely to respond to neoadjuvant therapies; chemotherapy regimens, choice of neoadjuvant chemotherapy in regard to tumor subtype; Her2-directed therapy, role of trastuzumab, lapatinib and combined Her2 blockade in the preoperative setting; antiangiogenesis treatment, use of bevacizumab, a monoclonal VEGF inhibitor in the neoadjuvant setting; and endocrine, choice of preoperative endocrine therapy and comparison of endocrine and chemotherapy.

Patient selection

Patients with locally advanced breast cancer are suitable candidates for neoadjuvant therapy because their cancers are often not initially resectable. This usually applies to patients with stage IIIA/IIIB or T3/T4 tumors (including tumors of any size with direct extension to the chest wall

and/or the skin and inflammatory breast cancer) and those with involvement of ipsilateral supra or infraclavicular lymph nodes (N3). Patients with early-stage breast cancer may be appropriate for neoadjuvant therapy if breast-conservation surgery (BCS) is not possible due to a high tumor-to-breast ratio, the breast cancer subtype is associated with a high likelihood of response and the patient is expected to require postoperative chemotherapy.

Tumor biology

Breast cancer is a heterogeneous disease with widely varied outcomes and response to standard therapies. Preoperative treatment has been established as most suitable for tumors likely to have a good response. The identification of immunohistochemical and gene markers and response to neoadjuvant therapy are under investigation as possible predictive factors for response to therapy. In general:

- Negative hormonal receptor (HR) status has emerged as the strongest predictive factor identified to date. Higher pathologic complete response (pCR) rates demonstrated in estrogen receptor (ER)-negative cancers may be four-times as high compared with ER-positive cancers in some neoadjuvant trials [2];
- Patients whose tumors achieve a pCR with neoadjuvant chemotherapy have a prognosis that is better than that predicted for the stage and receptor status of their disease.

Gene expression studies have identified several distinct breast cancer subtypes that differ markedly in prognosis and in the therapeutic targets they express. Three main subtypes include:

- Luminal subtypes are the most common, making up the majority of ER-positive breast cancer and are characterized by expression of ERs, progesteron receptors and other genes associated with ER activation. In regard to neoadjuvant chemotherapy:
  - They tend to have low sensitivity to this type of therapy
  - Although they have a low rate of pCR (<10%), they have a better

Pathologic complete response (pCR): absence of any residual invasive cancer in the resected breast specimen and axillary lymph nodes following completion of neoadjuvant systemic therapy (American Joint Committee on Cancer staging system). This definition is now well established but has varied between trials.

Her2: protein encoded by the *ERBB2* gene (member of the EGF-receptor family). Amplification or overexpression of this gene plays an important role in the pathogenesis and progression of breast cancer.

outcome than triple-negative or Her2-positive tumors
  - High tumor grade and young age may identify a subgroup who could benefit from neoadjuvant chemotherapy in these luminal subtypes
- Her2-enriched subtype comprises the majority of clinically Her2-positive breast cancer and represents 10–15% of breast cancer. The I-SPY 1 trial is a multicenter neoadjuvant breast cancer study [3]. The results showed that in Her2-positive breast cancer:
  - The pCR rate following neoadjuvant chemotherapy was higher in contrast with Her2-negative breast cancer regardless of HR status
  - The addition of trastuzumab to chemotherapy increased the pCR rate (60%)
  - Attainment of pCR is associated with improvement in overall survival
  - The addition of targeted treatment against Her2 (trastuzumab) to neoadjuvant chemotherapy is now standard care
- Triple-negative breast cancer (TNBC) represents 15–20% of all breast cancer. Characterized by low expression of HR-related genes and tumors that completely lack HRs and Her2 overexpression. In general, these tumors have the following clinical characteristics:
  - An aggressive clinical course, advanced stage and high histological grade at diagnosis
  - Increased risk of mortality within 5 years of diagnosis
  - Higher sensitivity to neoadjuvant chemotherapy, pCR rates can exceed 40%
  - Those who achieve pCR appear to have a prognosis similar to patients with other breast cancer subtypes who achieve a pCR
  - If there is more than minimal residual disease at surgery there is a much higher risk of early distant disease recurrence

Chemotherapy regimens

Neoadjuvant chemotherapy regimens most commonly contain an anthracycline (adriamycin or epirubicin) in combination or sequentially administered with taxanes (paclitaxel or docetaxel). Anthracycline-based regimens also usually include cyclophosphamide with or without fluoropyrimidines. Prior to the development of molecularly targeted therapies, unselected breast

Triple-negative breast cancer: more commonly diagnosed in women less than 40 years of age compared with hormone receptor-positive breast cancer. Up to 20 % of patients harbor a *BRCA* mutation (<6% of all breast cancers are associated with a *BRCA* mutation).

cancer populations were treated with chemotherapeutics acting indiscriminately on rapidly dividing cells. Targeted agents, including trastuzumab (Herceptin® [Genentech; CA, USA]), interfere with molecular pathways, driving tumor growth and progression, and were developed for use in subsets of patients expressing relevant biomarkers. Utilization of targeted therapies in biologically preselected patient populations has significantly improved survival. For example, in Her2-positive disease, sequential anthracycline–taxane-based chemotherapy in combination with trastuzumab gives a pCR of 38% compared with 19% with the chemotherapy alone [4].

In TNBC, the frequency of BRCA1/2 germline and somatic mutations is approximately 20%. As BRCA1/2 are critical regulators of DNA repair and maintenance of genomic stability, it was hypothesized that TNBC may be particularly sensitive to agents that cause DNA damage, including platinum-containing compounds (cisplatin and carboplatin) that induce synthetic lethality in repair defective cells via inhibition of poly (ADP-ribose) polymerase (PARP) pathways. In the unselected TNBC population, a modest benefit for platinum monotherapy has been shown, with platinum doublet/triplet chemotherapy showing more promise. Studies have shown pCR rates of 55% with neoadjuvant docetaxel and carboplatin [5], 40% with epirubicin, cisplatin and fluorouracil, followed by weekly paclitaxel [6]. The poor prognosis of TNBC without a pCR after neoadjuvant chemotherapy stresses the importance of the development of efficacious new therapies. There is currently an interest in targeting the enzyme PARP, which is involved in base-excision repair after DNA damage. PARP inhibitors have shown encouraging clinical activity in tumors arising in *BRCA* mutation carriers and in sporadic triple-negative cancers. PARP inhibitors are being investigated in the neoadjuvant setting in a number of small Phase II studies.

Her2-directed therapy

Some of the currently available Her2 targeted agents are shown in **Table 4.1**.

Trastuzumab

Breast cancers with Her2 over-expression or amplification were associated with poorer prognosis. In combination with chemotherapy, trastuzumab has shown remarkable efficacy in the metastatic and adjuvant setting, has improved prognosis and is now standard of care. Trastuzumab is generally administered until disease progression in the metastatic setting and for 1 year in the adjuvant setting.

Trastuzumab has more recently established a role in the neoadjuvant setting. All patients should resume

Table 4.1. Her2-targeted therapies in breast cancer.

Agent	Administration	Type of agent	Mechanism of action
Trastuzumab	Intravenously	Humanized monoclonal antibody	Binds intravenously to the extracellular domain of Her2
Lapatinib	Oral	Tyrosine kinase Inhibitor	Inhibitor of the intracellular tyrosine kinase domains of both EGF receptor and Her2 receptors
Pertuzumab	Intravenously	Humanized monoclonal antibody	Her2 dimerization inhibitor by binding to the extracellular domain II of Her2
Trastuzumab-DM1	Intravenously	Antibody–drug conjugate. Monoclonal antibody trastuzumab linked to the cytotoxic agent mertansine (DM1)	Trastuzumab binds to the extracellular domain of Her2, leading to intracellular delivery of DM1 activity by binding to Her2

DM1: Myatansinoid.

trastuzumab following surgery and complete a 52-week course. A meta-analysis of two randomized studies evaluated the benefit of adding concomitant trastuzumab to neoadjuvant (anthracycline/taxane-based) chemotherapy [7]. Eligible patients were randomized to receive either neoadjuvant chemotherapy alone or with concurrent administration of trastuzumab. The addition of trastuzumab doubled the rate of a pCR (43 vs 20%), significantly reduced the risk of relapse (25 vs 39%) and there was a trend towards a lower mortality rate (13 vs 20%). While the approved formulation of trastuzumab is administered intravenously (30–90 min), a subcutaneous preparation has been developed showing similar efficacy and only takes 5 min to administer [8].

Trastuzumab can cause left ventricular cardiac dysfunction, arrhythmias, hypertension, cardiac failure and cardiomyopathy. Cardiac toxicity is the only significant adverse effect of trastuzumab, but in trials this was usually reversible, and cardiac deaths were very rare. Analysis of three randomized trials in the neoadjuvant

setting showed that concurrent use of anthracycline-based chemotherapy and trastuzumab was associated with an increased risk of cardiac toxicity (overall response: 1.95; 95% CI: 1.16–3.29) [9], and therefore sequential use of these agents is currently recommended. It is recommended to monitor cardiac function (echo or multigated acquisition scan) prior to and during trastuzumab treatment.

Not all patients benefit from trastuzumab, with approximately 15–25% of women relapsing after trastuzumab-based therapy, indicating the presence of *de novo* or acquired resistance [10]. This is the basis for exploration into additional Her2-targeted therapeutics, including lapatinib, pertuzumab and trastuzumab myatansinoid (T-DM1). For more information, please see **Chapter 6**.

Lapatinib

For patients with Her2-positive breast cancer, the use of lapatinib is currently investigational in the neoadjuvant setting. Evidence from Phase III clinical trials in combination with chemotherapy as neoadjuvant [11] and first-line metastatic treatment [12] suggested that in direct comparison with trastuzumab, lapatinib is inferior in terms of efficacy.

In the neoadjuvant GeparQuinto Phase III trial, the efficacy and safety of the addition of lapatinib versus trastuzumab to anthracycline–taxane-based neoadjuvant chemotherapy was assessed [11]. Patients with Her2-positive operable or locally advanced breast cancer were treated with epirubicin plus cyclophosphamide for four cycles and then randomly assigned to treatment with docetaxel plus either trastuzumab or lapatinib. Treatment with chemotherapy plus trastuzumab resulted in a significantly higher rate of pCR compared with lapatinib (30 vs 23%) and was associated with less serious adverse events. Lapatinib use was associated with toxicities such as diarrhea and skin rash.

Combined Her2 blockade

Administration of dual Her2-targeted treatments with neoadjuvant chemotherapy is a promising new approach in Her2-positive patients, designed to overcome trastuzumab resistance. Trials of dual blockade are summarized in **Table 4.2**.

Lapatinib plus trastuzumab

Two randomized studies showed significant improvements in pCR rates with the addition of lapatinib to the combination of chemotherapy and trastuzumab.

In the Neo-ALTTO study, women with stage II–III breast cancer were randomly assigned to lapatinib, trastuzumab, or the combination of trastuzumab plus

Table 4.2. Trials of combined Her2 blockade.

Trial	Patients (n)	Phase	Neoadjuvant chemo-therapy	Her2 targeting	Weeks	Pathologic complete response; breast and axilla (%)	Ref.
NeoALTTO	455	III	Paclitaxel	Arm A: trastuzumab Arm B: lapatinib Arm C: trastuzumab and lapatinib	18	Arm A: 29 Arm B: 25 Arm C: 51	[13]
CHER-LOB	121	II	Paclitaxel and fluorouracil, epirubicin, and cyclo-phosphamide	Arm A: trastuzumab Arm B: lapatinib Arm C: trastuzumab and lapatinib	24	Arm A: 25 Arm B: 26 Arm C: 47	[14]
NeoSphere	417	II	Arm A, B, C: docetaxel Arm D: no chemotherapy	Arm A: trastuzumab Arm B: pertuzumab Arm C: pertuzumab and trastuzumab Arm D: pertuzumab and trastuzumab	12	Arm A: 22 Arm B: 18 Arm C: 39 Arm D: 11	[15]

lapatinib for 6 weeks, followed by the addition of paclitaxel for 12 weeks prior to surgery [13]. In terms of the pCR, dual blockade was significantly more efficacious (51%) than lapatinib (25%) or trastuzumab (29%) alone. This effect was seen in both ER-positive and -negative subgroups. Despite these results, the rate of BCS was unchanged. No major cardiac dysfunctions occurred. During the initial 6-week biological window, Her2-targeted treatment was given without chemotherapy, enabling a collection of samples for translational research, and early tumor response to be assessed without confounding by cytotoxic therapy.

In the CHER-LOB trial, patients received weekly paclitaxel followed by fluorouracil, epirubicin and cyclophosphamide chemotherapy and were randomly assigned to treatment with lapatinib, trastuzumab or both [14]. The pCR rate in patients who received dual Her2-targeted therapy was 47% (25%, and 26% in patients who received trastuzumab and lapatinib, respectively). The rate of BCS was not significantly different across the three arms. In both Neo-ALLTO and CHER-LOB, the incidence of diarrhea increased in patients who received lapatinib.

Pertuzumab & trastuzumab

Pertuzumab is a monoclonal antibody that binds to the extracellular domain II of Her2. Its mechanism of action is complementary to trastuzumab. Whereas trastuzumab blocks Her2 cleavage and inhibits ligand-independent signalling, pertuzumab exerts its effects by inhibiting ligand-dependent signalling, particularly between Her2 and Her3, which is known to activate a potent cell survival and proliferation signal. Both antibodies induce antibody-dependent cell-mediated cytotoxic effects. Pertuzumab has shown antitumor activity in both the metastatic and the neoadjuvant settings and is now being tested as adjuvant therapy.

The NeoSPHERE neoadjuvant trial, evaluated the combination of pertuzumab with docetaxel and trastuzumab [15]. Patients given pertuzumab and trastuzumab plus docetaxel (arm C) had a significantly improved pCR rate (39%) compared with those given trastuzumab plus docetaxel, without substantial differences in tolerability. A higher pCR in ER-negative than in ER-positive tumors was seen. In arm C, patients with ER-negative disease attained a pCR of 63% compared with 26% for patients with ER-positive cancer. Interestingly, pertuzumab and trastuzumab without chemotherapy eradicated tumors (pCR: 11%) in some women and showed a favorable safety profile, suggesting there may be a subgroup of patients who can

be spared chemotherapy. For more information, please see Chapter 6.

Future of Her2 targeting

An exciting development is the innovative approach to Her2 targeting by the targeted intracellular delivery of potent antitumor agent via a highly specific monoclonal antibody. T-DM1 consists of the trastuzumab antibody conjugated to DM1, which represents a maytansine derivative and binds to Her2 with an affinity similar to trastuzumab. After binding, T-DM1 is internalized and DM1 is released into the cell, thus delivering chemotherapy directly to cells over expressing Her2. DM1 leads to cancer cell death by inhibiting assembly of microtubules. T-DM1 has shown extremely encouraging clinical antitumor activity (response rates and survival) in patients with Her2-positive metastatic breast cancer whose cancer has progressed despite trastuzumab-based chemotherapeutic regimens. Limited toxicity was seen and many typical side effects of cytotoxic regimens were avoided [16]. Studies are ongoing in the neoadjuvant and adjuvant setting as monotherapy, in combination with chemotherapy and as dual blockade (pertuzumab).

Antiangiogenesis treatment

Bevacizumab is a recombinant, humanized, monoclonal anti-VEGF antibody that targets angiogenesis, vascular permeability and endothelial cell growth. Its synergy and efficacy with other chemotherapeutic agents in metastatic breast cancer has been shown in Phase III trials, although its role in this setting is yet to be established. Data with bevacizumab in the neoadjuvant setting are limited to date. Neoadjuvant bevacizumab, when added to standard chemotherapy for operable breast cancer, improved the rate of pCR in two large, multicenter, randomized trials (German Breast Group GeparQuinto [17] and USA NSABP B-40 [18]). Each trial involved women with Her2-negative breast cancer, who received four cycles of anthracycline-based and four cycles of taxane-based neoadjuvant chemotherapy, with or without the addition of bevacizumab. The NSABP trial also examined whether the addition of antimetabolite chemotherapy (capecitabine or gemcitabine) would be helpful. The key findings from these two trials are summarized in Table 4.3. In each study, the addition of bevacizumab

Angiogenesis: process of new blood vessel formation, plays a central role in both local tumor growth and distant metastasis in breast cancer. VEGF is a signal protein produced by cells that stimulates angiogenesis.

Table 4.3. Breast cancer trials of neoadjuvant bevacizumab.

Trial details	GeparQuinto [17]		NSABP B–40 [18]	
	Chemo-therapy (n = 974)	Chemotherapy + bevacizumab (n = 974)	Chemotherapy (n = 602)	Chemotherapy + bevacizumab (n = 604)
Neoadjuvant chemo-therapy regimen	Epirubicin/ cyclophosphamide → docetaxel		Docetaxel, docetaxel/capecitabine or docetaxel/gemcitabine → doxorubicin/cyclophosphamide	
pCR; breast and lymph nodes (%)	18	22	23	28
Significance	p = 0.07		p = 0.08	
Breast conservation (%)	62	62	45	47
Significance	Not significant		Not significant	

pCR: Pathologic complete response.

led to a nonstatistically significant improvement in the rate of pCR.

Although these results are promising, treatment with chemotherapy and bevacizumab also led to a significant increase in serious toxicities, including hypertension, hand-foot syndrome and mucositis, although there was no major increase in surgical complications. Subset analyses suggested high-grade tumors were more likely to achieve pCR with addition of bevacizumab in both trials. However, in the NSABP trial, ER expression was associated with greater relative benefit from bevacizumab, whereas in the GeparQuinto study, efficacy was restricted primarily to patients with TNBC. In the NSABP trial, the addition of capecitabine or gemcitabine to docetaxel therapy, compared with docetaxel therapy alone, did not significantly increase the rate of pCR and led to increased toxicity. The use of bevacizumab in the neoadjuvant setting remains unclear due to the modest incremental benefits and uncertain long-term effects on disease recurrence. Further research is needed to identify clear predictive biomarkers of response to bevacizumab that will help in selecting patients who may benefit from the addition of this drug.

Endocrine

Historically, neoadjuvant endocrine therapy was limited to patients with

endocrine-response disease but not medically fit, or refused chemotherapy and surgery. The relative lack of side effects in comparison with chemotherapy makes primary endocrine therapy an attractive option in this population:

- Patients are more likely to benefit from neoadjuvant endocrine therapy if the tumors express high levels of ER
- There are limited data with neoadjuvant endocrine therapy in premenopausal women, and therefore currently investigational in this population

Choice of endocrine therapy

Tamoxifen, an ER antagonist, has demonstrated efficacy for HR-positive early breast cancer in the adjuvant setting and several studies have indicated a potential benefit as initial hormonal therapy in locally advanced and operable breast cancer. Early Phase II studies in the elderly reported response rates of 49–68% [19].

Aromatase inhibitors (AIs) block the conversion of androgens to estrogens and reduce estrogen levels in tissue and plasma. The third-generation AIs (e.g., anastrozole, letrozole and exemestane) have shown clear superiority over tamoxifen in the adjuvant and metastatic setting. A meta-analysis supports their role in the neoadjuvant setting, with higher BCS rates compared with tamoxifen (response rate: 1.36; 95% CI: 1.16–1.59; $p < 0.001$) [20]. Letrozole is the most commonly used AI in this setting, although exemestane and anastrozole have been shown to have similar efficacy [21]. Optimal duration of treatment is not yet established it is but usually less than 9 months (37% achieve maximal response after 6–12 months) [22]. If there is evidence of progression or nonresponse then surgery is recommended.

Achievement of pCR is a valid surrogate of long-term survival; however, this is achieved in a minority of patients with ER-positive disease (2–10%). Higher ER levels correlate with a higher probability of response and a positive correlation has been found between ER level and degree of Ki-67 suppression (cell proliferation) during endocrine treatment [23].

Endocrine therapy versus chemotherapy

In general, chemotherapy is the preferred opinion in this setting; response to endocrine therapy was thought to take up to 3 months, although this may not always be the case. There are limited data comparing the effectiveness of neoadjuvant chemotherapy versus endocrine treatment. Data suggest that in ER-positive cancers, response

rate and rates of BCS may be similar [24]. Similar clinical response was shown between chemotherapy and endocrine treatment in tumors with low Ki-67, whereas tumors with high Ki-67 had a better response with chemotherapy [25]. There is now interest in defining groups of ER-positive breast cancer who would benefit from endocrine therapy or those that need chemotherapy. Future research may help to identify molecular markers that could predict long-term efficacy of neoadjuvant endocrine treatment.

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Multiple choice questions

1. Which of the following statements is correct regarding neoadjuvant treatment of breast cancer?
   - a. Neoadjuvant chemotherapy enables breast conservation surgery in all responders
   - b. Response rate is highest in estrogen receptor (ER)-positive breast cancers
   - c. Pathologic complete response usually correlates with improved survival for that subgroup of breast cancer
   - d. Neoadjuvant chemotherapy should be considered for all patients that prefer breast conservation surgery who would otherwise require a mastectomy
2. Regarding triple-negative breast cancer, which of the following are correct?
   - a. Patients who do not achieve a pathologic complete response following neoadjuvant chemotherapy have a worse survival compared with complete responders
   - b. Over 50% harbor a *BRCA* mutation
   - c. Platinum (DNA damaging) agents are preferred to anthacycline–taxane chemotherapy regimens for all patients with triple-negative breast cancer
   - d. Bevacizumab (VEGF inhibitor) has shown activity in this group of breast cancers and should be included in neoadjuvant chemotherapy regimes
3. Which of the following statements regarding Her2-directed agents in the neoadjuvant treatment of breast cancer is incorrect?
   - a. Patients with Her2-positive breast cancer who require neoadjuvant chemotherapy should be considered for treatment that includes trastuzumab
   - b. Trastuzumab has been associated with an increase in the incidence of cardiac dysfunction

c. To avoid cardiac impairment, concomitant use of trastuzumab and anthracycline chemotherapy should be avoided

d. The addition of pertuzumab to chemotherapy and trastuzumab significantly increases the risk of cardiac dysfunction compared with chemotherapy and trastuzumab alone

4. Which of the following statements is correct regarding the use of neoadjuvant endocrine treatment of breast cancer?

a. Aromatase inhibitors have better outcomes (breast conservation rate) compared with tamoxifen

b. Is beneficial only in ER/progesterone receptor-negative breast cancer

c. Tumors with high grade/Ki-67 (proliferation) tend to respond better to endocrine compared with cytotoxic agents

d. In comparison with chemotherapy, endocrine treatment is preferred in the elderly due to the likelihood of higher responses in this population

5. Which of the following statements is incorrect regarding the use of neoadjuvant treatment of breast cancer?

a. Neoadjuvant chemotherapy has shown a survival advantage compared with the same therapy after surgery

b. The preoperative setting gives a window of opportunity to assess sensitivity and resistance to standard and novel therapies

c. Some patients with breast cancers that have low tumor grade and are strongly ER positive could be considered for endocrine therapy instead of chemotherapy

d. For tumors that do not respond or grow during endocrine treatment, it is recommended to consider surgery

Clinical Insights

CHAPTER 5

Role of radiation after neoadjuvant chemotherapy

Michelle A Kraay & Janice A Lyons

Contents

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About the authors

Michelle A Kraay

Michelle A Kraay is an undergraduate at the University of Notre Dame (IN, USA) studying biology, with the goal of entering medical school upon graduation. She spent the summer with JA Lyons learning about the care and treatment of breast cancer. During this time, she was able to work in the operating room seeing breast reconstructive surgery, reading breast imaging studies with radiology staff and seeing a wide variety of breast cancer patients in the medical oncology and radiation oncology departments. She also coauthored a manuscript comparing different techniques for cardiac sparing during left sided breast irradiation and worked on a protocol looking at the safety of intraoperative radiation for patients undergoing oncoplastic reconstruction, in addition to coauthoring this book chapter.

Janice A Lyons

Janice A Lyons received her undergraduate degree at Duke University (NC, USA), where she majored in mathematics and psychology. She received her MD at the University of Illinois at Chicago College of Medicine (USA). Following medical school, she did her internship and residency in radiation oncology at the Cleveland Clinic Foundation (OH, USA), where she was chief resident for 2 years. She remained on staff at the Cleveland Clinic until 2003 when she took a position at University Hospitals Case Medical Center (OH, USA), where she is an Associate Professor and Director of Breast Services for the Department of Radiation Oncology. She is also the institutional Principle Investigator for the Radiation Therapy Oncology Group and is very active in breast cancer research. Her main research focus involves cardiac-sparing techniques for left-sided breast cancer. She has a strong interest in teaching and has served as Radiation Oncology Residency Program Director since 2007.

Learning points

After reading this chapter you will know:

- A significant benefit from the addition of postmastectomy radiation after neoadjuvant chemotherapy has been seen in some breast cancer patients.
- Both clinical and pathologic stages can play a role in decision-making for radiation after neoadjuvant chemotherapy, thus it is important to adequately stage patients prior to starting neoadjuvant therapy so that appropriate recommendations can be made.
- All patients undergoing breast conservation following neoadjuvant chemotherapy require radiation to at least the breast.
- Patients presenting with clinical stage III disease or patients with clinical T4 disease should receive postoperative radiation regardless of the response to neoadjuvant chemotherapy.
- Response rates seen in neoadjuvant chemotherapy using newly developed agents can aid determination of the effectiveness of the therapy using fewer patients than conventionally required for clinical trials, thus reducing the cost of the trial and limiting the need for long-term follow-up.

Summary

The use of neoadjuvant chemotherapy in breast cancer continues to increase in frequency. There are many potential advantages to this approach in women who require chemotherapy. One advantage is the ability to shrink the tumor for patients who would otherwise require a mastectomy, thus increasing the potential for breast conservation [1–4]. For patients presenting with node-positive disease, there is the potential to render the patient node-negative at the time of surgery, potentially allowing for less axillary surgery, and in turn, lower complication rates, most notably lymphedema. As new chemotherapy and biologic agents are developed, response rates to neoadjuvant chemotherapy can help determine the effectiveness of the therapy with less patients needed for clinical trials, thus reducing the cost of the trial

and limiting the need for long-term follow-up. In the past, decisions involving the role of radiation as well as the field arrangement have been made based on pathology at presentation. With this increased use of neoadjuvant chemotherapy, radiation recommendations can be a little more challenging requiring excellent communication between the surgical, medical and radiation oncology providers.

Decision-making

Many patient- and tumor-related factors influence the recommendation for radiation after neoadjuvant chemotherapy. Both clinical stage and pathologic stage can play a role in decision-making, thus it is important to adequately stage patients prior to starting neoadjuvant therapy so that appropriate recommendations can be made.

There have been many studies that have demonstrated improved outcomes with the addition of radiation to the breast after breast-conserving surgery [5–9]. For patients who are undergoing breast-conserving surgery following neoadjuvant chemotherapy, radiation to the breast is always indicated. The decision to add radiation to the regional lymph nodes or to recommend radiation after mastectomy is more controversial. The rest of this chapter will focus on the recommendations for postmastectomy radiation, with the assumption that similar field arrangements should be recommended for patients undergoing breast conservation.

Clinical stage

A study by physicians at Jackson Memorial Hospital, University of Miami (FL, USA) investigated the role of postmastectomy radiation in patients with clinical stage III disease that were initially treated with neoadjuvant chemotherapy [10]. Outcomes were analyzed based on calculated rates of locoregional recurrence (LRR), defined as any recurrence to the chest wall area or to the regional lymphatics, namely the axillary, internal mammary, infraclavicular or supraclavicular nodes. Of the 13 patients who did not receive

Neoadjuvant chemotherapy: the primary systemic treatment received by nonmetastatic breast cancer patients before surgery.

Breast-conserving surgery: also known as quadrantectomy, this is less radical than mastectomy and radiation to the breast is recommended in cases of breast-conserving surgery.

any radiation, four experienced a LRR (31%). Of the 42 patients receiving radiation, only three experienced a LRR (7%). Notably, one of these patients relapsed in an area that had been left out of the radiation field. The patients receiving radiation displayed an improved overall survival. This study concluded that the addition of postmastectomy radiation improved locoregional control in patients with clinical stage III disease receiving neoadjuvant chemotherapy.

Subsequent studies have provided more specific details regarding which breast cancer patients gain a significant benefit from the addition of postmastectomy radiation after neoadjuvant chemotherapy. A retrospective study performed by physicians at MD Anderson Cancer Center (TX, USA) included 150 patients who had been treated with neoadjuvant chemotherapy followed by mastectomy without radiation [11]. It was found that a larger clinical tumor size and combined stage at the time of diagnosis predicted for higher rates of LRR. At the time of surgery, the number of positive lymph nodes and the size of the residual tumor were both independent factors that predicted for LRR. The study also found that the use of tamoxifen was linked to lower rates of LRR in patients.

Another large, retrospective study from the MD Anderson Cancer Center compared the outcomes of breast cancer patients treated with neoadjuvant chemotherapy followed by mastectomy with patients treated with initial mastectomy followed by adjuvant chemotherapy [12]. None of the patients included in this study had received radiation. The rates of LRR for any pathologic tumor size (measured at the time of surgery) were found to be higher for the patients who received neoadjuvant chemotherapy. This discrepancy was thought to be present because during neoadjuvant chemotherapy, it is likely for the tumor to shrink in size or disappear completely. In these cases, the pathologic size of the residual tumor may be significantly smaller than the size it was observed to be clinically, or at the time of diagnosis. This gives the physician a somewhat lacking representation of the disease to be treated. It is also less likely, but still possible, for positive nodes to change their status during neoadjuvant chemotherapy. For these reasons, it is important that the radiation oncologist considers both the clinical and pathologic T and combined stages. The study concluded that radiotherapy should be offered to all patients receiving neoadjuvant chemotherapy with clinical stage T3 (>5 cm) breast cancer, four or more positive lymph nodes at surgery, or clinical combined stage III or greater disease.

A third retrospective study carried out at the MD Anderson Cancer

Center included 542 patients treated with neoadjuvant chemotherapy, mastectomy and radiation [13]. The data acquired from these patients was compared with data from 134 patients who received neoadjuvant chemotherapy followed by mastectomy without radiation. Those who received postmastectomy radiotherapy were shown to have a significantly lower 10-year rate of LRR (11 vs 22%, p = 0.0001). Radiation was also shown to reduce the rate of LRR in patients who were judged to have a clinical stage III–IV disease and subsequently reached a pathologic complete response (pCR) after neoadjuvant chemotherapy. A major conclusion of this study was that in patients with clinical T3 tumors or clinical stage III–IV disease and in patients with four or more positive nodes, radiation was found to be beneficial. Based on the results of this study, radiation should be offered to patients that fall into these categories, regardless of their response to neoadjuvant chemotherapy.

Another subsequent study by Huang *et al.* reviewed the outcomes of 542 patients with clinical stage II–IV disease treated with neoadjuvant chemotherapy, mastectomy and postmastectomy radiation [14]. The study identified five factors that were associated with higher rates of LRR in the study's population: involvement of the skin or nipple; supraclavicular nodal disease; extracapsular extension in the lymph nodes; negative estrogen receptor status; and no tamoxifen use. Patients with three or more of these factors were thought to have a clinically relevant risk of LRR (defined as a LRR of greater than 10%) and, based on the study's results, would benefit from postmastectomy radiation.

Patient-related factors

Young age as a risk factor

A total of 132 patients with stage I or II disease at diagnosis were included in a retrospective study at the MD Anderson Cancer Center that examined their treatment outcomes after receiving neoadjuvant chemotherapy without postmastectomy radiation [15]. The study found that patients with tumor size >5 cm, four or more pathologically positive lymph nodes or aged 40 years or younger had a significantly higher risk of LRR. Patients with any of these factors are recommended to undergo

Pathologic complete response: disappearance of the initial tumor described by the pathologist after primary systemic treatment.

postmastectomy radiation treatment (Figure 5.1). Patients with T1 or T2 stage tumors and one to three involved lymph nodes did not have a clinically relevant risk of LRR without radiation. Therefore, the study concluded that these patients would not see a significant benefit in undergoing radiation.

A second review by Garg *et al.* further investigated the risk associated with young age [16]. The retrospective study included 107 breast cancer patients that were younger than 35 years old at the time of diagnosis and had clinical stage II–III disease. All patients were treated with neoadjuvant chemotherapy and mastectomy. In total, 18 out of 80 patients receiving postmastectomy radiation had a LRR (22.5%), while ten patients out of the 27 individuals who did receive any radiation had a LRR (37%). A significant improvement in locoregional control and overall survival was noted in the patients who received radiation compared with those who did not.

HEGF receptor 2-positive disease

It has been suggested that cancer cells that overexpress or have amplified expression of the HEGF receptor (HER2) are radioresistant. Physicians at the MD Anderson Cancer Center investigated whether a patient's HER2 status was connected to their risk of LRR [17]. Patients included in this retrospective study were all treated with neoadjuvant chemotherapy, mastectomy and radiation, and initially screened for *HER2* overexpression or amplification. When compared, the 5- and 10-year rates of LRR in the patients with HER2-positive disease and the patients with HER2-negative disease were not significantly different.

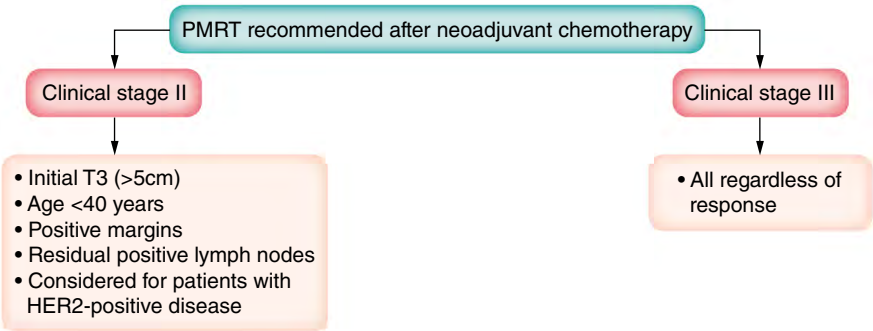

Figure 5.1. Patients who would benefit from postmastectomy radiation therapy.
PMRT: Postmastectomy radiation therapy.

A retrospective study included patients with stage II–III and HER2-positive breast cancer who were treated with neoadjuvant chemotherapy [18]. The majority of these patients (94.3%) had a chemotherapy regimen that included trastuzumab, an antibody that targets the HER2/neu receptor. By comparing the outcomes of patients treated with radiation to those of who had forgone radiation treatment, it was found that radiation significantly reduced the risk of LRR, adding to the benefits seen from trastuzumab.

Pathologic stage

Physicians and researchers at the MD Anderson Cancer Center have investigated the effect of radiation on patients who had a pCR to neoadjuvant chemotherapy [19]. A breast cancer patient with a pCR would, at the time of surgery, have no remaining tumor cells and no involved lymph nodes. For patients who were initially diagnosed with stage III breast cancer, the addition of postmastectomy radiation lowered the 10-year rate of LRR from 33% without the use of radiation to 7.3% with radiation, $p = 0.040$. The study found that the addition of radiation did not significantly improve the rates of LRR for patients achieving a pCR with clinical stage I or II disease. Based on the results of this study, radiation should be recommended for patients diagnosed with combined stage III breast cancer who have since achieved a pCR to neoadjuvant chemotherapy.

Daveau *et al.* retrospectively reviewed the outcomes of a large population of breast cancer patients who had, following neoadjuvant chemotherapy and at the time of breast-conserving surgery, no involved lymph nodes [20]. These individuals were said to have pathologic N0 status (pN0). Patients who had clinical N3 status were excluded from this study. Of the patients included in this study, 36.3% were treated with radiation to the breast alone and 63.7% received treatment to both the breast and the regional lymph nodes. The treatment with breast irradiation alone did not significantly increase the rate of LRR in these patients who had achieved pN0 status. It was concluded that radiation to the regional lymph nodes may not be necessary for this subset of breast cancer patients.

A study from the same hospital included 134 patients with clinical stage II or III disease who had achieved pN0 status after neoadjuvant chemotherapy [21]. These patients all underwent mastectomy, with 58.2% continuing on to receive postmastectomy radiation. There was no significant difference in the rates of LRR or the overall survival of patients who received radiation compared with those who did not. Patients who did not achieve a pCR to neoadjuvant chemotherapy had a significantly lower overall survival rate. The results of this study

suggest that patients who achieve pN0 status after neoadjuvant chemotherapy may not need to receive postmastectomy radiation. This question is currently being investigated by a cooperative group trial through the National Surgical Adjuvant Breast and Bowel Project and the Radiation Therapy Oncology Group.

A prospective study by Mamounas *et al.* gathered a large population of breast cancer patients who received neoadjuvant chemotherapy and analyzed their outcomes in order to identify predictors of LRR [22]. Patients who had clinical T4 tumors or clinical N2 status were excluded from this study. The patients who underwent breast-conserving surgery were treated with adjuvant radiation to the breast only, while the patients who underwent mastectomy did not receive radiation. This study found that patients who had pN0 status and a pCR at the time of surgery had low rates of LRR, regardless of age, clinical tumor stage and clinical combined stage. This differs from previous findings [19]. These results still need to be verified by ongoing prospective studies.

Conclusion

Many factors play a role in the recommendation for postoperative radiation in the setting of neoadjuvant chemotherapy. All patients undergoing breast conservation following neoadjuvant chemotherapy require radiation to at least the breast. The inclusion of regional lymph node coverage depends on many clinical and pathologic factors. Patients presenting with clinical stage III disease or patients with clinical T4 disease (skin involvement, inflammatory breast cancer or chest wall involvement) should receive postoperative radiation regardless of the response to neoadjuvant chemotherapy. For patients presenting with clinical stage I and II disease, the recommendation for adding postoperative radiation to the breast/chest wall and regional lymph nodes should be individualized based on the response to chemotherapy. Young patients, patients with residual nodal disease, presence of extranodal extension, inability to achieve negative margins and significant residual disease in the breast should all be considered for comprehensive nodal irradiation following neoadjuvant chemotherapy. Patients who present with lymph node-positive disease that are rendered negative by neoadjuvant chemotherapy, may not need nodal irradiation and radiation can potentially be omitted following mastectomy. Ongoing studies will help clarify this for us.

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Multiple choice questions

1. Radiation should be offered to which of the following patients, regardless of their response to neoadjuvant chemotherapy?
   - a. Patients with clinical T3 tumors
   - b. Patients with clinical stage III–IV disease
   - c. Patients with four or more positive nodes
   - d. All of the above
2. Which of the following is correct?
   - a. All patients undergoing breast conservation following neoadjuvant chemotherapy require radiation to at least the breast
   - b. Patients undergoing breast conservation following neoadjuvant chemotherapy should receive radiation based on response
   - c. Patients undergoing breast conservation following neoadjuvant chemotherapy do not require radiation therapy
3. Which patient would not require postmastectomy radiation following neoadjuvant chemotherapy?
   - a. A 50-year-old female with a clinical 3-cm, estrogen receptor-positive breast cancer who achieved a pathologic complete response (pCR)
   - b. A 65-year-old female with a clinical 6-cm, node-positive breast cancer who achieved a pCR
   - c. A 55-year-old female with a clinical 3-cm, node-negative breast cancer who had 2.5 cm of residual cancer with two out of 12 positive lymph nodes
   - d. A 45-year-old female with an inflammatory breast cancer who achieved a pCR
4. Clinically relevant risk of locoregional recurrence (LRR) is defined as:
   - a. A LRR of less than 10%
   - b. A LRR of greater than 10%
   - c. A LRR of 10%

Clinical Insights

CHAPTER 6

Monoclonal antibody therapy

Jean-Sébastien Frenel & Mario Campone

Contents

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Learning points

After reading this chapter you will know:

- Trastuzumab is the only monoclonal antibody approved in the neoadjuvant setting in breast cancer, in combination with chemotherapy for human EGF receptor 2 (HER2)-positive breast cancer.
- Strong biologic data support the concept of dual HER2 blockade, with different anti-HER2 agents, demonstrating complementary mechanisms of action to overcome resistance, currently being investigated in the neoadjuvant setting.
- High pathologic complete response rate can be obtained by the combination of two targeted therapies, raising the opportunity of a chemotherapy-free approach for selected breast cancer subtypes.
- Pertuzumab, a humanized monoclonal antibody that blocks the dimerization of HER2 with HER1, 3 and 4, and trastuzumab–emtansine, a HER2-targeted antibody–drug conjugate, are very promising drugs in the neoadjuvant setting for HER2-positive breast cancer.
- Neoadjuvant bevacizumab improves pathologic complete response in breast cancer, but the data on survival are still too immature to justify its use in the neoadjuvant setting.

Summary

Over the past 10 years, concurrent efforts in the identification of the major pathways involved in tumor progression and the development of molecules has led to the approval of five new targeted therapies, in addition to chemotherapy or endocrine therapy, in the field of breast cancer. The introduction of trastuzumab into clinical practice changed the natural course of human EGF receptor 2 (HER2)-positive breast cancer, and this treatment has been approved in the adjuvant, neoadjuvant and metastatic settings. Besides trastuzumab, monoclonal antibodies pertuzumab and trastuzumabemtansine have recently been approved in the metastatic setting of HER2-positive disease,

while bevacizumab is approved in the metastatic setting of HER2-negative disease. Numerous clinical trials are ongoing and attempting to push these treatments in the neoadjuvant setting, while addressing the question of the best chemotherapeutic agents to associate with. In this chapter, the authors review the current and forthcoming data on the use of monoclonal antibodies as part of neoadjuvant therapy.

Neoadjuvant human EGF receptor 2-targeted therapies in human EGF receptor 2-positive breast cancer

Trastuzumab is the only monoclonal antibody approved in the neoadjuvant setting in breast cancer

Trastuzumab is a recombinant, monoclonal IgG_1 class, humanized, murine antibody directed against human EGF receptor 2 (HER2). Trastuzumab is approved for the treatment of HER2-positive early breast cancer, in combination with neoadjuvant chemotherapy followed by adjuvant herceptin therapy, for locally advanced (including inflammatory) disease or tumors >2 cm in diameter.

Four randomized trials have tested the addition of trastuzumab to chemotherapy in the neoadjuvant setting, with various chemotherapy regimens leading to a pathologic complete response (pCR) ranging from 26 to 65% versus 19–28% for the same chemotherapeutic agent in monotherapy **(Table 6.1)** [1–4]. Although trastuzumab-based therapies have been associated with increased incidence of cardiac dysfunction, especially when combined with anthracyclines, three large clinical trials have evaluated the concurrent

Pathologic complete response (pCR): in clinical trials, pCR has been used as a surrogate marker for clinical outcome (including overall survival) for patients receiving neoadjuvant treatment. The most widely accepted definition of pCR is 'no residual invasive carcinoma in the breast and axillary lymph nodes' but less stringent definitions are used in some neoadjuvant trials. A standardized definition of pCR should be utilized for all clinical trials and panelists at the National Cancer Institute State-of-the-Science Conference on Preoperative Therapy in 2007 recommended that the preferred definition of pCR is 'the absence of residual invasive cancer within both the breast and lymph nodes' [17].

Table 6.1. Randomized trials of neaoadjuvant chemotherapy plus or minus trastuzumab.

Author (year)	Patients (n)	Treatment arm	Chemotherapy regimen	pCR (%)		Ref.
				Breast	Breast + lymph node	
Buzdar *et al.* (2005)	42	A	Paclitaxel (×4) - FEC75 (×4)	26	NP	[1]
		B	Paclitaxel (×4) + trastuzumab (12weeks) - FEC75 (×4) + trastuzumab (12 weeks)	65	NP	
Gianni *et al.* (2010)	235	A	Adriamicine + paclitaxel (×3) - paclitaxel (×4) - CMF (×3)	22	19	[2]
		B	Adriamicine + paclitaxel + tastuzumab (×3) - paclitaxel + trastuzumab (×4) - CMF + trastuzumab (×3)	43	38	
Pierga *et al.* (2010)	120	A	Epirubicine + cyclophosphamide (×4) - docetaxel (×4)	19	NP	[3]
		B	Epirubicine + cyclophosphamide + trastuzumab(×4) - docetaxel (×4) + trastuzumab (×12)	26	NP	
Steger *et al.* (2009)	90	A	Epirubicin + docetaxel (×6) ± capecitabine (×6)	26	NP	[4]
		B	Epirubicin + docetaxel (×6) ± capecitabine (×6) + trastuzumab (×6)	40	NP	

CMF: Cyclophosphamide, methotrexate and 5-fluoro-uracil; FEC: Fluorouracil, epirubicin and cyclophosphamide; NP: Not provided; pCR: Pathologic complete response.

administration of anthracycline-based chemotherapy and trastuzumab in the neoadjuvant setting. None of these trials have demonstrated a significant increase in short-term cardiac toxicity and the trastuzumab label has recently been changed by the EMA to include treatment in combination with neoadjuvant chemotherapy, which could contain an anthracycline: "in patients with early breast cancer eligible for neoadjuvant–adjuvant treatment, trastuzumab should only be used concurrently with anthracyclines in chemotherapy-naive patients and only with low-dose anthracycline regimens (maximum cumulative doses: 180 mg/m^2 doxorubicin or 360 mg/m^2 epirubicin). If patients have been treated concurrently with low-dose anthracyclines and herceptin in the neoadjuvant setting, no additional cytotoxic chemotherapy should be given after surgery" [101]. However, no study has yet demonstrated a significant improvement in pCR rate or any survival endpoint from the addition of a HER2-targeted agent to both the anthracycline and taxane portion of a regimen versus the taxane portion alone, or indeed to taxane-based chemotherapy plus a HER2-targeted agent in the absence of an anthracycline. According to EMA recommendations, cardiac safety should be monitored every 3 months during treatment and every 6 months for 24 months following discontinuation of treatment. Patients treated with anthracycline should be monitored for longer, yearly up to 5 years from the last administration of herceptin [101].

Current development of trastuzumab partner

The introduction of trastuzumab into clinical practice has changed the natural course of HER2-positive breast cancer. However, in the metastatic setting, disease progression on trastuzumab occurs inevitably and metastatic HER2-positive disease remains mostly incurable. Several strategies have been developed in the metastatic setting to overcome the resistance, and strong biologic data support the concept of dual HER2 blockade [5], with different anti-HER2 agents demonstrating complementary mechanisms of action (Table 6.2) [6–10]. Recently, two new monoclonal antibodies, pertuzumab and trastuzumabemtansine (TDM-1) have been approved in HER2-positive metastatic breast cancer in addition to or as a substitution of trastuzumab. These components are currently evaluated in the neoadjuvant setting.

Pertuzumab

Pertuzumab, is also a humanized monoclonal antibody, but, unlike trastuzumab, it sterically blocks the dimerization of HER2 with HER1, 3 and 4. These different molecular

Table 6.2. Randomized trials comparing human EGF receptor-2-targeting approaches.

Study (year)	Patients (n)	Treatment arm	Chemotherapy regimen	Breast	Breast + lymph node	Ref.
Combination with lapatinib						
NeoALLTO (2012)	455	A	Trastuzumab (6 weeks) - trastuzumab + paclitaxel (12 weeks)	29.5	27.6	[6]
		B	Lapatinib (6 weeks) - lapatinib + paclitaxel (12 weeks)	24.7	20	
		C	Trastuzumab + lapatinib (6 weeks) - trastuzumab + lapatinib + paclitaxel (18 weeks)	46.8	46.8	
GeparQuinto (2012)	615	A	EC + trastuzumab (×4) - docetaxel + trastuzumab (×4)	34.2	30.3	[7]
		B	EC (×4) + lapatinib (12 weeks) - docetaxel (×4) + lapatinib (12 weeks)	26	22.7	
CHER-LOB (2012)	80	A	Paclitaxel + trastuzumab (12 weeks) - FEC75 (×4) + trastuzumab (12 weeks)	NP	25	[9]
		B	Paclitaxel + lapatinib (12 weeks) - FEC75 (×4) + lapatinib (12 weeks)	NP	26.3	
		C	Paclitaxel + lapatinib + trastuzumab (12 weeks) - FEC75 (×4) + lapatinib + trastuzumab (12 weeks)	NP	46.7	

EC: Epirubicin and cyclophosphamide; FEC: Fluorouracil, epirubicin and cyclophosphamide; NP: Not provided; pCR: Pathologic complete response.

Table 6.2. Randomized trials comparing human EGF receptor-2-targeting approaches.

Study (year)	Patients (n)	Treatment arm	Chemotherapy regimen	Breast	Breast + lymph node	Ref.
Combination with lapatinib (cont.)						
Holmes *et al.* (2011)	100	A	Trastuzumab (2 weeks) - FEC75 (×4) + trastuzumab (12 weeks) - paclitaxel + trastuzumab (12 weeks)	54	NP	[8]
		B	Lapatinib (2 weeks) - FEC75 (×4) + lapatinib (12 weeks) - paclitaxel + lapatinib (12 weeks)	45	NP	
		C	Trastuzumab + lapatinib (2 weeks)- FEC75 (×4) + trastuzumab + lapatinib (12 weeks) - paclitaxel + trastuzumab + lapatinib (12 weeks)	74	NP	
Combination with pertuzumab						
NeoSphere (2012)	417	A	Docetaxel + trastuzumab (×4)	31	23	[10]
		B	Docetaxel + trastuzumab + pertuzumab (×4)	49	42	
		C	Trastuzumab + pertuzumab (×4)	18	12	
		D	Docetaxel + pertuzumab (×4)	23	17	
TRYPHANEA (2013)	225	A	FEC100 + pertuzumab + trastuzumab (×3) - docetaxel + pertuzumab + trastuzumab (×3)	61	50.7	[12]
		B	FEC100 (×3) - docetaxel + pertuzumab + trastuzumab (×3)	57.3	45.3	
		C	Docetaxel + carboplatin + pertuzumab + trastuzumab (×6)	66.2	51.9	

EC: Epirubicin and cyclophosphamide; FEC: Fluorouracil, epirubicin and cyclophosphamide; NP: Not provided; pCR: Pathologic complete response.

features provide the biologic rationale for combining trastuzumab with pertuzumab for a more complete HER2 blockade. Pertuzumab has recently been approved in combination with trastuzumab and docetaxel chemotherapy for the treatment of HER2-positive metastatic breast cancer in patients who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease. This approval is based on data from the Phase III CLEOPATRA study, which demonstrated a 38% reduction in the risk of disease progression or death compared with standard therapy (hazrd ratio: 0.62; $p < 0.0001$) in 808 women with previously untreated HER2-positive metastatic breast cancer or that had recurred after prior therapy in the adjuvant or neoadjuvant setting [11]. The study demonstrated a 6.1-month improvement in median progression-free survival, with a median progression-free survival of 18.5 versus 12.4 months. The Phase II NeoSphere trial has addressed the combination of trastuzumab and pertuzumab in the neoadjuvant setting [10]. Patients with locally advanced, inflammatory or early HER2-positive breast cancer were randomized between four arms of 12-week treatment: trastuzumab–pertuzumab–docetaxel; trastuzumab–docetaxel; pertuzumab–docetaxel; or trastuzumab–pertuzumab. The primary end point was pCR in the breast, defined as the absence of invasive residual disease. The pCR rate was 45.8% in the triple-association arm (trastuzumab–pertuzumab–docetaxel) and 29, 24 and 16.8% in the trastuzumab–docetaxel,pertuzumab–docetaxel, and trastuzumab–pertuzumab arms, respectively. The pCR was significantly increased in hormone receptor-negative tumors (27.3%), with the combination of the two monoclonal antibodies suggesting an opportunity of a chemotherapy-free regimen in selected subgroups. Toxicity was mainly docetaxel related in the docetaxel-containing arms with grade 3 neutropenia, febrile neutropenia. Cardiac tolerance was good with a 5% of mean decrease in left ventricular ejection fraction, with not significant difference with the addition of pertuzumab to trastuzumab.

The Phase II trial TRYPHAENA randomized patients between the experimental arms of: (group 1) fluorouracil, epirubicin and cyclophosphamide, followed by docetaxel with pertuzumab–trastuzumab during the whole treatment period; or (group 2) during the taxane part of the chemotherapy; or (group 3) docetaxel–carboplatin with the pertuzumab–trastuzumab combination during the whole neoadjuvant phase [12]. The cardiac toxicity, which was the primary end point, was not found to be different between the three experimental arms. The pCR rates ranged from 57 to 66% in the three arms.

Trastuzumabemtansine

T-DM1 is a HER2-targeted antibody–drug conjugate, composed of trastuzumab, a stable thioether linker, and the potent cytotoxic agent derivative of maytansine (DM1). This compound has recently been approved following results from the Phase III EMILIA study, which randomized T-DM1 alone or lapatinib in combination with capecitabine in 991 people with HER2-positive, locally advanced breast cancer or metastatic breast cancer previously treated with trastuzumab and a taxane chemotherapy [13]. The study met both coprimary efficacy end points of overall survival and progression-free survival (median overall survival: 30.9 months versus 25.1 months and 32% risk reduction of death; hazrd ratio: 0.68; p = 0.0006). T-DM1 is currently being investigated in the neoadjuvant setting. TDM4874g, a single-arm, open-label, Phase II study, assessed the clinical safety of T-DM1 following anthracycline-based chemotherapy in the adjuvant or neoadjuvant setting for early stage HER2-positive breast cancer. The use of T-DM1 for four cycles after anthracycline-based chemotherapy was not associated with clinical cardiac toxicity and final analyses, including long-term cardiac toxicity and pCR, were published in October 2013 [14].

Dual blockade of HER2 with the combination of trastuzumab with small inhibitors

Lapatinib is a dual tyrosine kinase inhibitor, which selectively binds to HER1 and HER2 receptors intracellularly to prevent the phosphorylation of downstream pathways that activate cell proliferation and survival. Lapatinib is approved in the metastatic setting and has been demonstrated to share complementary mechanisms of anti-HER2 action and non-cross-resistant with trastuzumab, supporting their combination.

Four neoadjuvant studies, with a treatment arm that included a trastuzumab and lapatinib combination, have reported results on pCR rate [6–9]. The international Phase III NeoALTTO study randomized 455 patients with locally advanced HER2-positive breast cancer to three treatments arms: oral lapatinib (1500 mg/d); trastuzumab (4 mg/kg loading dose, 2 mg/kg subsequent doses); or lapatinib (1000 mg/d) plus trastuzumab for a total of 6 weeks and then with in combination with paclitaxel for 12 weeks until surgery. The pCR, defined as the absence of invasive tumor in breast, was significantly higher in the combined lapatinib–trastuzumab arm (51.3%) versus 29.5% (p = 0.0001) and 24.7% in the trastuzumab and lapatinib arms, respectively. It is worth noting,

the trastuzumab and lapatinib arms were found to be similar in terms of pCR (p = 0.34). The toxicity was mainly lapatinib related, but in terms of cardiac safety no major decrease in left ventricular ejection fraction was reporter. The Phase II CHER-LOB study is a Phase II trial that randomized preoperative taxane–anthracycline chemotherapy with lapatinib (arm A), trastuzumab (arm B) or lapatinib–trastuzumab (arm C) in HER2-positive breast cancer. The pCR rate, defined as the absence of invasive tumor in the breast and axillary lymph nodes, was 36.2% overall (28% in arm A; 32% in arm B; and 48% in arm C), once again favoring the dual HER2 blockade strategy. However, it this was a noncomparative study not permitting comparisons between the arms. The high pCR with combination therapy also came with increased adverse events, such as diarrhea (grade 3: 2.7% in arm A; 33% in arm B; and 34.8% in arm C), dermatologic toxicities (grade 3: 5.5% in arm A; 12.8% in arm B; and 10.8% in arm C), and hepatic toxicities (grade 3: 2.7% in arm A; 12.8% in arm B; and 4.3% in arm C). The protocol starting doses of lapatinib were subsequenltly amended for arms B and C, where lapatinib was reduced from 1500 to 1250 mg and from 1000 to 750 mg, respectively. However, despite dose reductions, 30% of patients from arm B and 17% from arm C discontinued the trial due to adverse reactions, and 43.6% in arm B and 54% in arm C had to schedule breaks in their treatment.

Taken together, these studies show that the combined trastuzumab–lapatinib regimen results in increased pCR, which is an important end point for HER2-positive breast cancer, but at the cost of greater toxicity. Without mature data on disease-free and overall survival from these neoadjuvant trials, trastuzumab in combination with lapatinib is not a standard of care in the neoadjuvant setting. Major concerns remain on the therapeutic index of the lapatinib and trastuzumab combination, with regard to the favorable pattern of toxicity of the pertuzumab or TDM-1. Nevertheless, the high pCR rate obtained by the combination of two targeted therapies raises the opportunity of a chemotherapy-free approach, which could be useful for treatment of the controversial T1aT1b (<1 cm), HER2-positive operable breast cancer, where no standard of care has yet been established with a prospective, randomized clinical trial.

Antiangiogenic monoclonal antibody-based therapy in the neoadjuvant setting

Targeting angiogenesis has emerged as a potential therapeutic approach for breast cancer. Numerous targeted therapies with variable mechanisms of action to block the VEGF pathway have been investigated.

Table 6.3. Neodjuvant bevacizumab: outcomes in GeparQuinto and NSABP B-40.

Trial (year)	Patients (n)	Treatment arm	Chemotherapy regimen	pCR (%)		Ref.
				Breast	Breast + lymph node	
GBG44 (2012)	42	974	Epirubicin + cyclophosphamide + docetaxel	20.6	18.3	[15]
		974	Epirubicin + cyclophosphamide + docetaxel + bevacizumab	24.6	21.7	
NSABP-403 (2010)	235	602	Docetaxel or docetaxel–capecitabine or docetaxel–gemcitabine or doxorubicine + cyclophosphamide	28.2	34.5	[16]
		604	Chemotherapy + bevacizumab	23	27.6	

pCR: Pathologic complete response.

Bevacizumab, a humanized monoclonal antibody with binding specificity for VEGF, was approved in 2008 in metastatic breast cancer following several randomized trials, which demonstrated an increased response rate with the addition of bevacizumab to chemotherapy in first- and second-line metastatic breast cancer and, for some of them, a significantly improved progression-free survival. However, the lack of demonstrated overall-survival benefit led to the withdrawal of its US FDA approval in the USA and in Canada in 2011, arguing a lack of favorable cost–effectiveness with regard to an increased toxicity.

Bevacizumab has been logically investigated in the neoadjuvant setting and the primary objective of both the GBG44 and NSABP B-40 trials was to determine whether combining bevacizumab with various chemotherapy regimens would significantly improve the rate of pCR in women with nonmetastatic HER2-negative breast cancer **(Table 6.3)** [15,16]. Both studies showed significant improvements in the rate of pCR, which was defined differently: GBG44 trial defined it as the absence of residual

tumor in the breast and nodes, and the NSABP B-40 trial used the less stringent definition of the absence of residual tumor in the breast only. The addition of bevacizumab in the GBG44 study resulted in an increase of 3.5 percentage point pCR rate ($p = 0.04$), whereas in the NSABP B-40 study, the magnitude of the benefit was 6.3 percentage point pCR rate with bevacizumab ($p = 0.02$). However, when the more stringent definition of pCR was used, the differences noted in the NSABP B-40 were no longer significant. Conflicting results were shown in subgroup analyses. In the GBG44 trial, the rates of pCR were significantly increased with bevacizumab therapy in patients with triple-negative breast cancer, whereas in the NSABP B-40 trial there was only a trend favoring bevacizumab in that population. By contrast, the NSABP B-40 trial demonstrated a significant increase in the rate of pCR in patients with hormone receptor-positive cancer, whereas in the GBG44 trial, no differences were noted in that population. An analysis of survival is still premature in both trials.

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Multiple choice questions

1. Trastuzumab is approved...
   a. In neoadjuvant setting with any chemotherapy including anthracycline
   b. In combination with pertuzumab in the neoadjuvant setting
   c. In monotherapy in the neoadjuvant setting
2. Pathologic complete response in breast cancer after neoadjuvant treatment...
   a. Is often used as a surrogate end point for neoadjuvant chemotherapy
   b. Is defined in all the trials by 'no residual invasive carcinoma in the breast and axillary lymph nodes'
   c. Is demonstrated as a surrogate marker for overall survival
3. Dual blockade of human EGF receptor 2 (HER2)...
   a. Is a strategy currently developed to overcome resistance to trastuzumab
   b. Is a strategy currently developed to increase pathologic complete response in neoadjuvant treatment of breast cancer
   c. Could lead to chemotherapy-free approach for subgroup of breast cancer
4. Pertuzumab...
   a. Blocks the dimerization of HER2 with HER1, 3 and 4
   b. Has been investigated in the neoadjuvant setting in the NeoSphere and NeoALLTO trials
   c. Is approved in the metastatic setting
5. Antiangiogenic therapies in neoadjuvant setting....
   a. Are recommended for all HER2-negative neoadjuvant patients
   b. Increase overall survival
   c. Use bevacizumab as a VEGF Trap

Multiple choice questions: ANSWERS

Chapter 2. Evaluation of complete pathologic response

1. Concerning neoadjuvant chemotherapy, which of the following is true?
   a. Neoadjuvant chemotherapy (NAC) is indicated in inflammatory breast cancers
2. Regarding pathological response, which of the following is true?
   b. pCR is known to show a strong association with disease-free survival and overall survival
3. One of the statements regarding pathological techniques is false, which is it?
   c. A full inclusion of the mastectomy specimen is always made
4. Which of these sentences concerning the pathological response is not true?
   a. Triple-negative breast cancers have low pCR rates
5. Concerning the effect of systemic treatment on pCR, we can say that which of the following is true:
   c. Use of targeted therapies in a neoadjuvant setting improves pCR rates

Chapter 3. Recommendation and predictors of pathologic response

1. Which of the following is the goal of neoadjuvant systemic therapy?
   a. To improve surgical options
   b. To acquire early information on response and biology of the disease
2. Neoadjuvant chemotherapy is more effective...
   c. In patients with hormone receptor-negative tumors with high proliferation rate

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3. Which of the following pathology results after surgery is associated with best overall survival results?
   c. Complete absence of invasive and noninvasive cancer, both in the breast and in the lymph nodes studied after surgery
4. The addition of the drugs targeting HER2-pathway to the neoadjuvant chemotherapy scheme in HER2-positive patients improves
   a. Pathologic complete response rate
   b. Event-free survival
5. What factors determine the risk of local recurrence after completion of neoadjuvant chemotherapy and surgery?
   a. Initial stage
   b. Intrinsic subtype

Chapter 4. Combination chemotherapy and targeted agents

1. Which of the following statements is correct regarding neoadjuvant treatment of breast cancer?
   c. Pathologic complete response usually correlates with improved survival for that subgroup of breast cancer
2. Regarding triple-negative breast cancer, which of the following are correct?
   a. Patients who do not achieve a pathologic complete response following neoadjuvant chemotherapy have a worse survival compared with complete responders
3. Which of the following statements regarding Her2-directed agents in the neoadjuvant treatment of breast cancer is incorrect?
   d. The addition of pertuzumab to chemotherapy and trastuzumab significantly increases the risk of cardiac dysfunction compared with chemotherapy and trastuzumab alone
4. Which of the following statements is correct regarding the use of neoadjuvant endocrine treatment of breast cancer?
   a. Aromatase inhibitors have better outcomes (breast conservation rate) compared with tamoxifen

5. Which of the following statements is incorrect regarding the use of neoadjuvant treatment of breast cancer?
   a. Neoadjuvant chemotherapy has shown a survival advantage compared with the same therapy after surgery

Chapter 5. Role of radiation after neoadjuvant chemotherapy

1. Radiation should be offered to which of the following patients, regardless of their response to neoadjuvant chemotherapy?
   d. All of the above
2. Which of the following is correct?
   a. All patients undergoing breast conservation following neoadjuvant chemotherapy require radiation to at least the breast
3. Which patient would not require postmastectomy radiation following neoadjuvant chemotherapy?
   a. A 50-year-old female with a clinical 3-cm, estrogen receptor-positive breast cancer who achieved a pathologic complete response (pCR)
4. Clinically relevant risk of locoregional recurrence (LRR) is defined as:
   b. A LRR of greater than 10%

Chapter 6. Monoclonal antibody therapy

1. Trastuzumab is approved...
   a. In neoadjuvant setting with any chemotherapy including anthracycline
2. Pathologic complete response in breast cancer after neoadjuvant treatment...
   a. Is often used as a surrogate end point for neoadjuvant chemotherapy
3. Dual blockade of human EGF receptor 2 (HER2)...
   a. Is a strategy currently developed to overcome resistance to trastuzumab
   b. Is a strategy currently developed to increase pathologic complete response in neoadjuvant treatment of breast cancer
   c. Could lead to chemotherapy-free approach for subgroup of breast cancer

4. Pertuzumab...
   c. Is approved in the metastatic setting
5. Antiangiogenic therapies in neoadjuvant setting....
   c. Use bevacizumab as a VEGF Trap