The goal of preoperative pharmacotherapy in patients with breast cancer is to enable breast conserving surgery in stage T3N0-1M0 or radical mastectomy in patients with primary inoperative tumors (T1-4N0-3M0). The choice of optimal treatment should be based not only on risk factors resulting from the stage but also on predicted cancer responsiveness to the treatment. The breast cancer subtypes defined by immunohistochemical profile (expression of ER, PR, HER2 and Ki67) are characterized by different responsiveness to therapy. Complete response confirmed by histopathological evaluation after neoadjuvant chemotherapy is a positive prognostic factor in some breast cancer subtypes. This marker is not of value in postmenopausal patients with ER/PR+ HER2– tumors, who are candidates for neoadjuvant hormone therapy. These patients have a good prognosis if in a histopathological report after surgery there are features such as pT1, pN0, Ki67 < 3%, and ER Allred score ≥ 3. The goal of the paper is to present current knowledge about preoperative pharmacotherapy of breast cancer.

Key words: preoperative systemic treatment, complete pathological response, breast cancer subtypes.

Contemp Oncol (Pozn) 2016; 20 (2): 93–101
DOI: 10.5114/wo.2016.60067

The role of preoperative systemic treatment in patients with breast cancer

Sylwia Dębska-Szmich, Magdalena Krakowska, Urszula Czernek, Maja Habib-Lisik, Agnieszka Zięba, Piotr Potemski

Department of Chemotherapy, Chair of Oncology, Medical University of Lodz, Poland

Introduction

Chemotherapy, hormonal therapy and molecular targeted therapy are important elements of breast cancer treatment. Systemic treatment is indicated in patients with locally or regionally advanced cancer. It is also the basic treatment of metastatic breast cancer. In patients with operable breast cancer, preoperative chemotherapy has the same value as postoperative treatment regarding disease-free survival (DFS) and overall survival (OS) [1].

Primary systemic therapy plays the crucial role in treatment of patients with inoperable tumors (TNM stage III, excluding T3NI). Neoadjuvant therapy can induce a tumor response and enable radical surgery. This type of treatment is of value also in patients with primary operable cancer, when after tumor shrinkage breast conserving surgery (BCS) becomes possible (T3N0-I).

During the planning of systemic treatment it is important to consider not only the stage of the disease but also its biological character determining sensitivity of cancer cells to the medicaments.

This paper is a review of the literature dedicated to the optimal preoperative systemic treatment in patients with breast cancer and presents current knowledge of the topic.

Making a diagnosis

According to the current guidelines of the European Society of Medical Oncology (ESMO) the goals of preoperative systemic treatment in patients with breast cancer are [2]:

- To enable breast conserving surgery in stage T3N0-1M0,
- To enable mastectomy in patients with primary inoperable breast cancer in stage IIIA–C and inflammatory breast cancer (T1-4N0-3M0),
- To obtain information about efficacy of pharmacotherapy and prognosis,
- To broaden the knowledge about biology and optimal treatment of breast cancer (clinical trials).

Before treatment an accurate diagnosis is essential. Information about histopathological type, receptor expression and staging should be obtained. Material for histopathological and immunohistochemical evaluation should be obtained from the tumor through core needle biopsy. A surgical specimen can also be taken.

In the case of axillary lymphadenopathy, fine needle biopsy of the lymph nodes should be performed. Histopathological evaluation should include assessment of histological type, grading, expression of hormonal receptors (estrogen receptors — ER, progesterone receptors — PR), HER2 and, according to current guidelines, Ki67.

To properly evaluate staging, imaging of the breast and axilla (mammography, ultrasound examination, US) is needed as well as tests to exclude distant metastases — especially in patients with stage III (liver and renal func-
tion tests, bone metabolism, full blood count, chest X-ray, abdominal US or CT, bone scintigraphy). If breast conserving surgery is planned, the tumor should be marked with skin tattooing or marker clips implantation.

According to the current guidelines of ESMO the choice of neoadjuvant chemotherapy should be based on the same predictive factors as in the adjuvant setting.

Systemic treatment should last 3–6 months. All 6–8 cycles of chemotherapy should be given before the operation. If the disease progresses during chemotherapy, treatment should be switched to another kind of therapy.

Currently the choice of pharmacotherapy in breast cancer is mostly based on predicted sensitivity of cancer cells to the medicaments than on risk of recurrence resulting from staging. Patients with hormonal receptor expression and HER2 negativity are prone to be more resistant to chemotherapy than ER-negative patients with HER2 overexpression or triple negative patients [3–5]. On the other hand, hormonal treatment is effective when there is expression of ER in tumor cells, so it may be a good therapeutic option in the first group of patients.

Moreover, the latest trials have shown that adding anti-HER2 medicaments to neoadjuvant chemotherapy is of value [3, 6].

After completion of neoadjuvant treatment the operation should be performed. Adjuvant treatment (radiotherapy, immunotherapy with trastuzumab, hormonal treatment) should be considered depending on the clinical situation, predictive factors and risk of recurrence [2].

This paper presents results of the most important research in the field of systemic neoadjuvant treatment in breast cancer and current practical guidelines in this domain.

Importance of complete response confirmed with pathologic examination after preoperative chemotherapy

Complete response confirmed with pathologic examination of a surgical resection specimen (pathologic complete response – pCR) is the result of effective neoadjuvant chemotherapy and is associated with a good prognosis in patients with some types of breast cancer.

One of the first papers which confirmed the good prognostic value of pCR was published by Kuerer et al. [7]. Three hundred and seventy two patient with breast cancer were eligible for the study. They were treated with preoperative chemotherapy (4 cycles of FAC – fluorouracil, doxorubicin, cyclophosphamide), then they underwent an operation (mastectomy or BCS and axillary lymphadenectomy) and were subsequently exposed to adjuvant treatment (chemotherapy, radiotherapy, hormonotherapy if indicated).

Sixteen percent of them (n = 60) achieved pCR in the primary tumor, and 12% (n = 43) in both the primary tumor and axillary lymph nodes. Pathologic complete response was more common in patients with ER-negative tumors (p < 0.001), high nuclear grading (p < 0.001) and with smaller primary tumors (p < 0.001). The 5-year overall survival rate was higher in patients with pCR than in patients with residual disease (89% vs. 64%, p = 0.003). The same pattern was observed regarding the 5-year disease-free survival rate (87% vs. 58%, p = 0.0005).

In another article Kuerer et al. [8] underlined good prognosis resulting from pCR in axillary lymph nodes after neoadjuvant chemotherapy. They compared survival of 43 patients with no evidence of cancer cells in axillary lymph nodes in pathological examination and of 148 patients with involved lymph nodes. Pathologic complete response was associated with higher rate of 5-year overall survival (87% vs. 58%, p = 0.00059) and disease-free survival (87% vs. 51%, p = 0.00003).

Therefore, a good prognosis in patients with breast cancer after neoadjuvant chemotherapy results from pCR in the primary tumor and in axillary lymph nodes. Loya et al. showed that a routine histological examination of axillary lymph nodes is sufficient, and the addition of immunohistochemical examination detecting occult metastases is not necessary [9]. They did not find a statistically significant difference in disease-free survival between breast cancer patients treated with neoadjuvant chemotherapy who had occult metastases in axillary lymph nodes and patients with eradiated cancer cells (p = 0.31).

Recently the positive prognostic value of pCR was confirmed by 2 meta-analyses. Cortazar et al. found that patients who achieved a pathological complete response had better overall and event-free survival [3]. They also found that eradication of invasive cancer from both breast and lymph nodes was better associated with improved event-free survival (EFS) and OS than was eradication from the breast alone. Similarly, von Minckwitz et al. in their meta-analysis of 7 German neoadjuvant trials demonstrated that pCR defined as eradication of tumor from both breast and lymph nodes strongly correlated with DFS in higher risk groups (ductal, high grade, hormonal receptors negative, HER2-positive, triple-negative), but not in patients with luminal A-like and ER+/HER2+ tumors [10].

It is worth emphasizing that pCR can only be confirmed with histopathological examination, but not with clinical or radiological examination. Croshaw et al. [11] assessed accuracy of different imaging methods and clinical examination in determining postneoadjuvant pathologic tumor response. Sixty one patients who underwent preoperative chemotherapy or hormonal therapy were eligible for the study. Only in 54% of patients was a complete response confirmed by radiological or clinical examination was concordant with the pathological report. Moreover, in patients younger than 50 years this rate was even lower. This paper demonstrates the difference between clinical and histological methods in determining tumor response to systemic treatment.

According to the recommendations from an international consensus conference on neoadjuvant systemic therapy in primary breast cancer, the definition of pCR should be based on histopathological examination, including absence of invasive cancer in both breast and lymph nodes. The component of ductal carcinoma-in situ (DCIS) should be reported separately [12].
Optimal choice of preoperative chemotherapy

There are many articles dedicated to preoperative chemotherapy in breast cancer. Researchers demonstrated good prognostic value of pCR in aggressive subtypes of cancer, and it, also expresses the effectiveness of particular schemes of chemotherapy.

The trial by Rastogi et al. [13] compared 4 preoperative cycles of AC (doxorubicin, cyclophosphamide) (n = 804) or 4 cycles of AC plus 4 cycles of docetaxel (n = 805) with 4 preoperative cycles of AC and 4 postoperative cycles of docetaxel (n = 802) in patients with operable breast cancer (T1-3N0-1M0). The authors did not find a statistically significant difference in 8-year OS or DFS between these groups of patients. However, patients who had preoperative sequential AC and docetaxel had a higher rate of pCR than those who had only preoperative AC (26% vs. 13%, p < 0.001). Also, patients with pCR had a better 8-year survival rate than patients with residual disease (89.4% vs. 73.6%, p < 0.0001).

A benefit from adding taxanes to preoperative chemotherapy was not observed by Evans et al. [14]. The authors compared 2 regimens of neoadjuvant chemotherapy: 6 cycles of AC (n = 180) and 6 cycles of AT (doxorubicin, docetaxel) (n = 183). They did not find a statistically significant difference in pCR rate (16% vs. 12%, p = 0.43) or 3-year survival rate between groups.

Probably the beneficial effect of adding taxanes to preoperative chemotherapy arises from the fact that these drugs were given sequentially with an anthracycline-based scheme. Table 1 presents examples of studies in which taxanes were administered sequentially or simultaneously with anthracyclines [13, 15–17]. It is obvious that schemes with sequentially given taxanes produced almost a 2 times higher pCR rate than schemes with simultaneously given taxanes or regimens without taxanes. The highest pCR rate was observed in patients treated with weekly paclitaxel given sequentially with FAC – pCR was achieved in 28.2% of patients [17].

Very interesting data were presented by von Minckwitz et al. in their meta-analysis including 7 German neoadjuvant trials [6]. They demonstrated that the pCR rate was higher in patients who had an increased number of chemotherapy cycles, higher cumulative anthracycline doses, higher cumulative taxane doses and capecitabine-containing regimens. For particular breast cancer phenotypes different characteristics of neoadjuvant therapy were associated with a favorable outcome: the association of pCR with number of trastuzumab cycles (4 vs. 8–12 cycles; p = 0.39). According to the current guidelines of ESMO, preoperative chemotherapy with sequentially given anthracyclines and taxanes is recommended in patients with breast cancer [2]. All scheduled cycles should be administered before surgery. In HER2-positive patients, immunotherapy with trastuzumab should be started in the neoadjuvant setting in association with the taxane part of the chemotherapy regimen. This strategy increases the probability of achieving pCR.

Predictive factors for preoperative chemotherapy

Simultaneously with trials exploring the efficacy of different regimens of preoperative chemotherapy there have been a number of studies dedicated to identification of predictive factors. According to different authors, higher rate of pCR was associated with: hormonal receptors’ negativity [17–20], higher grading [18, 21], higher Ki67 expression [21], HER1 (EGFR) expression [21], HER2 overexpression [19, 20, 22], lack of BCL2 expression [12], lack of primary axillary lymphadenopathy [18], and at least 75% reduction of Ki67 expression after chemotherapy [23].

An article published by Sikov et al. showed that different patterns of ER, PR and HER2 expression are associated with different responses to preoperative chemotherapy; the highest pCR rate was achieved in patients with triple-negative breast cancer (TNBC) [20].

Subtypes of breast cancer were distinguished more than a decade ago and were based on genetic characteristics [24]. These subtypes have different clinical courses and prognoses. Due to difficulty in practical application of this genetic classification, the current ESMO guidelines recommend use of a classification based on immunohistochemical features such as expression of ER, PR, HER2 and Ki67. In spite of the fact that clinical subtypes adopted the genetic nomenclature, there are many differences between these two classifications. There are 5 immunohistochemical subtypes of breast cancer:

Table 1. Examples of studies exploring preoperative chemotherapy based on taxanes and anthracyclines administered sequentially or simultaneously

| Study | Treatment (N – number of patients) | Results – pCR rate |
|-------|----------------------------------|--------------------|
| B:27 Rastogi 2008 | N = 2411 AC 4× → AC 4× → AC 4× | AC – 13% vs. AC – 26% p < 0.0001 |
| [13] | | |
| GEPIARDUO von Minckwitz 2005 | N = 913 AT q2w 4× → AC q3w 4× → T q3w 4× | AT – 7% vs. AC – 14.3% p < 0.0001 |
| [15] | | |
| AGO Untch 2002 | N = 475 E q2w 3× → P q2w 3× → EP q3w 4× | E → P – 18% vs. EP – 10% p = 0.03 |
| [16] | | |
| Green 2005 | N = 258 P q1w 12× → FAC 4× → P q3w 4× → FAC 4× | P q1w – 28.2% vs. P q3w – 15.7% p = 0.02 |
| [17] | | |

AC – doxorubicin + cyclophosphamide; T – docetaxel; pCR – complete pathologic response; AT – doxorubicin + docetaxel; E – epirubicin; P – paclitaxel; EP – epirubicin + paclitaxel; q1w – given every 1 week; q2w – given every 2 weeks; FAC – fluorouracil + doxorubicin + cyclophosphamide.
the fact that breast cancer subtype can be predictive of response to preoperative chemotherapy depended on immunohistochemical subtype, but it also underlined the importance of histological subtype of breast cancer.

The rate of axillary pCR was seen in patients with TNBC or HER2-positive breast cancer. Histological subtype of breast cancer was confirmed in the above-mentioned meta-analyses. According to Cortazar et al., the frequency of pCR in patients with low-grade and hormone receptor-positive tumors was low, but it was increased in the high-grade hormone-receptor-positive subgroup and triple-negative and HER2-positive tumors. Within the HER2-positive population, pCR was more common for hormone-receptor-negative patients than for hormone receptor-positive ones [3]. The same conclusion was drawn by Houssami et al. [4].

In addition, Denkert et al. revealed that presence of tumor-associated lymphocytes in breast cancer was a significant independent predictive factor of response to neoadjuvant chemotherapy. Patients with lymphocyte-predominant breast cancer responded with pCR rates of 40–42%, while those with tumors without any infiltrating lymphocytes had pCR rates of 3–7% [30].

Another important issue is the prognostic value of achieving pCR. An article published by Fasching et al. [31] confirmed the positive prognostic value of pCR in patients with TNBC or HER2-positive subtype. Five-year OS rates in patients with TNBC were 89% vs. 58% (p < 0.01) in pCR and no-pCR groups, respectively, and in HER2-positive patients they were 100% vs. 66% (p = 0.02), respectively. But patients with HR+ HER2– tumors rarely had pCR, and in this group achieving pCR was not associated with prognosis (p = 0.92). These findings were confirmed in a meta-analysis by Cortazal et al.: the association between achieving pCR and long-term outcomes was strongest in patients with triple-negative breast cancer and in those with HER2-positive,
hormone-receptor negative tumors who received trastuzumab [3]. Additionally, von Minckwitz et al. reported that pCR strongly correlated with DFS in higher risk groups, but not in luminal A-like and ER+/HER2+ tumors [10].

Luminal A subtype of breast cancer is probably less sensitive to chemotherapy, and optimal systemic treatment (chemotherapy or hormonal therapy) in these patients needs to be identified.

**Optimization of primary systemic treatment based on breast cancer subtype**

Because of the diverse response of breast cancer subtypes to different methods of preoperative pharmacotherapy, it is of value to find optimal treatment for every group of patients.

As mentioned before, TNBC is highly responsive to chemotherapy. Referring to some biological similarities, this subtype is often identified with BRCA1-related breast cancer. In fact, reduced expression of BRCA1–mRNA is observed in 25% of TNBC patients, and it is mainly due to the promoter methylation [32]. Decreased activity of BRCA1 protein impairs damaged DNA repair. Cancers with this disorder are recognized as particularly sensitive to nucleic acid-damaging cytotoxics such as platinum compounds. This presumption led to research investigating the role of platinum-based chemotherapy in patients with TNBC or BRCA1-related breast cancer.

According to different authors, preoperative chemotherapy based on anthracyclines, taxanes or both produced a 12–38% pCR rate in patients with TNBC. Table 3 presents these studies as well as those exploring platinum-based chemotherapy [20, 27, 33–36]. On the other hand, Table 4 summarizes papers dedicated to preoperative chemotherapy in BRCA1- and BRCA2-related breast cancer [37–41]. In both tables the studies exploring platinum-based chemotherapy enrolled very small groups of patients (10–28 patients). Moreover, some of them were retrospective. It is possible that these facts influenced the surprisingly high rate of pCR. These data must be confirmed in a large, prospective clinical trial before recommendation of a platinum-based preoperative chemotherapy in patients with TNBC or BRCA1- and BRCA2-related breast cancer. As yet the results of two interesting trials are available. The Ge-parsixto study evaluated the benefit of adding carboplatin to paclitaxel plus non-pegylated liposomal doxorubicin given as a weekly regimen for 18 weeks to 595 patients with HER2-positive or triple-negative breast cancer. In the triple-negative subgroup pCR was achieved by 37.9% of the control arm and 58.7% of the carboplatin arm (P < .05) [42]. During San Antonio Breast Cancer Symposium 2013, Sikov et al. presented their study determining whether the

Table 3. Examples of studies exploring neoadjuvant chemotherapy in patients with TNBC

| Study                | Treatment                                      | Number of patients | pCR rate (%) |
|----------------------|------------------------------------------------|--------------------|--------------|
| Liedtke et al. 2008  | FAC/FEC/AC, T + FAC/T + FEC                    | 70                 | 20           |
|                     | Taxane monotherapy                             | 17                 | 12           |
| Carey et al. 2007   | AC                                             | 34                 | 27           |
| Wang et al. 2009    | AT                                             | 21                 | 38           |
| Sikov et al. 2009   | Carboplatin (AUC 6) + paclitaxel              | 12                 | 67           |
| Chang et al. 2010   | Carboplatin (AUC 6) + docetaxel                | 11                 | 54.6         |
| Silver et al. 2010  | Cisplatin                                      | 28                 | 22           |

AC = doxorubicin + cyclophosphamide, T = docetaxel, pCR = complete pathologic response, AT = doxorubicin + docetaxel, FAC = fluorouracil + doxorubicin + cyclophosphamide, fluoroaracil + epirubicin + cyclophosphamide

Table 4. Examples of studies dedicated to preoperative chemotherapy in BRCA1- and BRCA2-related breast cancer patients

| Study                | Treatment                                      | Number of patients | pCR fraction |
|----------------------|------------------------------------------------|--------------------|--------------|
| Byrski et al. 2009  | Cisplatin                                      | 10                 | 9/10         |
| Hubert et al. 2009  | Anthracycline-based chemotherapy               | 15                 | 2/15         |
| Arun et al. 2011    | AT                                             | 64                 | 21/46 (0.46) |
|                     | Anthracycline-based chemotherapy               | 14                 | 4/9 (0.44)   |
|                     |                                                 |                    | 3/18 (0.17)  |
|                     |                                                 |                    | 0/5          |
| Byrski et al. 2009  | CMF                                            | 14                 | 1/14         |
|                     | AT                                             | 25                 | 2/25         |
|                     | AC/FAC                                         | 51                 | 11/51 (0.22) |
|                     | Cisplatin                                      | 12                 | 10/12 (0.83) |
| Chappuis et al. 2002| Anthracycline-based chemotherapy               | 9                  | 4/9          |

CMF = cyclophosphamide, methotrexate, fluorouracil, AC = doxorubicin + cyclophosphamide, AT = doxorubicin + docetaxel, FAC = fluorouracil + doxorubicin + cyclophosphamide
be continued for 3–4 months. According to Mustacchi patients [47–49]. Preoperative hormone therapy should be more effective than with tamoxifen in postmenopausal patients revealed that treatment with aromatase inhibitors (IA) was more effective than treatment with letrozole for premenopausal patients [41]. The PROACT, P024 and Eiermann et al. studies reported a 20–79% objective response rate according to different chemotherapy regimens used. Endocrine therapy produced a 20–79% objective response rate compared to 20%–28% with tamoxifen in premenopausal patients and 24%–30% in postmenopausal patients [42]. A – 0 vs. TAM – 1 vs. A + TAM – 0 improvement of feasible surgery: A – 43% vs. TAM – 30.8%, p = 0.04

**PROACT**

Cataliotti et al. 2006 [47]

Postmenopausal, HT for 3 mo.,
A (n = 163) vs. TAM (n = 151)

ORR (USG):
A – 36.2% vs. TAM – 26.5%, p = 0.07

improvement of feasible surgery:
A – 43% vs. TAM – 30.8%, p = 0.04

**P024**

Ellis et al. 2007 [48]

Postmenopausal, HT for 4 mo.,
L (n = 154) vs. TAM (n = 170)

ORR (MMG):
L – 60% vs. TAM – 41%, p = 0.004

BCS rate:
L – 48% vs. TAM – 36%, p = 0.036

**Eiermann et al. 2001 [49]**

Postmenopausal, HT for 4 mo.,
L (n = 162) vs. TAM (n = 175)

ORR (USG):
L – 35% vs. TAM – 25%, p = 0.042

BCS rate:
L – 45% vs. TAM – 35%, p = 0.022

pCR rate:
L – 2/162 vs. TAM – 3/175

**Mustacchi et al. 2009 [50]**

N = 117 > 70 years
Exe 25 mg/d for 5 mo.

ORR after 3 mo. 44.7%
ORR after 6 mo. 69.6%

CR 0

**ACOSOG Z1031**

Ellis et al. 2011 [52]

Postmenopausal, HT for 4 mo.,
Exe (n = 124) vs. L (n = 127) vs. A (n = 123)

ORR:
Exe – 62.9%, L – 74.8%, A – 69.1%

BCS rate:
Exe – 67.8%, L – 60.8%, A – 77%

**Results**

| Study | Treatment (N, n – number of patients) | Results |
|-------|--------------------------------------|---------|
| Bergman et al. 1995 [44] | N = 85, TAM, age > 75 years, unknown HR expression | ORR = 14.1%, PR = 23.5% |
| Bradbeer et al. 1983 [45] | N = 161, age > 70 years, TAM | ORR = 61%, CR = 27% |
| IMPACT | Postmenopausal, HT for 3 mo., A (n = 113) vs. TAM (n = 108) vs. A + TAM (n = 109) | ORR (USG): A – 24% vs. TAM – 20% vs. A + TAM – 28% (NS) CR (USG): A – 0 vs. TAM – 1 vs. A + TAM – 0 |
| Smith et al. 2005 [46] | Postmenopausal, HT for 3 mo., A (n = 163) vs. TAM (n = 151) | ORR (USG): A – 36.2% vs. TAM – 26.5%, p = 0.07 |
| PROACT | Cataliotti et al. 2006 [47] | Postmenopausal, HT for 3 mo., A (n = 163) vs. TAM (n = 151) | ORR (USG): A – 36.2% vs. TAM – 26.5%, p = 0.07 |
| P024 | Ellis et al. 2007 [48] | Postmenopausal, HT for 4 mo., L (n = 154) vs. TAM (n = 170) | ORR (MMG): L – 60% vs. TAM – 41%, p = 0.004 |
| Eiermann et al. 2001 [49] | Postmenopausal, HT for 4 mo., L (n = 162) vs. TAM (n = 175) | ORR (USG): L – 35% vs. TAM – 25%, p = 0.042 |
| Mustacchi et al. 2009 [50] | N = 117 > 70 years, Exe 25 mg/d for 6 mo. | ORR after 3 mo. 44.7% |
| ACOSOG Z1031 | Ellis et al. 2011 [52] | Postmenopausal, HT for 4 mo., Exe (n = 124) vs. L (n = 127) vs. A (n = 123) | ORR: Exe – 62.9%, L – 74.8%, A – 69.1% |

**HR = hormone receptors, HT = hormone therapy, TAM = tamoxifen, A = anastrozole, L = letrozole, Exe = exemestane, CR = complete response, PR = partial response, ORR = overall response rate, BCS = breast conserving surgery, ORR (USG) = overall response rate measured by ultrasound, ORR (MMG) = overall response rate measured by mammography, NS = not significant**

Addition of either carboplatin or bevacizumab to neoadjuvant chemotherapy with sequential paclitaxel and dose dense doxorubicin and cyclophosphamide significantly improves the response rate in TNBC. Fifty percent of 221 patients treated with carboplatin achieved pCR compared to 41% of 212 patients without carboplatin [43].

Table 5 presents studies exploring the effectiveness of preoperative hormonal therapy in patients with breast cancer [44–51]. It is worth mentioning that pCR after preoperative hormonal therapy is a very rare phenomenon [44–51]. It is worth mentioning that pCR after preoperative hormonal therapy is a very rare phenomenon [44–51].

Because luminal A subtype is characterized by different biology compared with other subtypes and the prognostic value of achieving pCR is not applicable in this group of patients, a predictive factor for hormonal treatment as well as a prognostic factor is needed. A study by Ellis et al. [52,
The role of preoperative systemic treatment in patients with breast cancer was dedicated to this problem. On the basis of data from histopathological examination of a tumor specimen taken before and after neoadjuvant hormonal treatment, the authors calculated the PEPI score (preoperative endocrine prognostic index). It included pT, pN, decrease of Ki67 expression after systemic treatment and ER expression after preoperative hormone therapy. Smaller primary tumor, lack of lymph node involvement, bigger reduction of Ki67 expression and higher expression of ER after hormonal treatment produced lower a PEPI. The authors identified 3 prognostic groups of patients according to different PEPI scores (low risk – PEPI 0, intermediate risk – PEPI 1–3, high risk – PEPI ≥ 4). Patients eligible for the PO24 study from these prognostic groups had different 6-year recurrence free survival (90%, 77%, 52%, respectively; p < 0.001) and breast cancer-specific survival (98%, 89% and 83%, respectively; p < 0.001).

Although the PEPI needs to be validated prospectively, it underlines the different biology of hormone-dependent breast cancer and indicates the direction of further studies.

**Inflammatory breast cancer as a particular indication for primary chemotherapy**

Inflammatory breast cancer (IBC) is an indication for primary systemic treatment because skin involvement is categorized as T4. According to current guidelines [54] to diagnose inflammatory breast cancer the following criteria should be met:
- Rapid onset of breast erythema, edema or peau d’orange or warm breast with or without a palpable tumor,
- Erythema involving at least one-third of the breast,
- Duration of the symptoms less than 6 months,
- Microscopically confirmed invasive breast cancer.

It is obligatory to take a surgical specimen or perform a core biopsy for microscopic evaluation. Most experts also recommend skin punch biopsy to reveal characteristic dermal lymphatic invasion. Pathologist should always determine histological type of the tumor, its grading and expression of ER, PR and HER2.

For proper staging mammography and US of the breast and axilla are required. Currently magnetic resonance of the breast is not recommended as a routine diagnostic method. However, all patients with IBC should have CT of the chest and abdomen and bone scintigraphy to exclude distant metastases. It is not recommended to perform routine PET or PET-CT.

Inflammatory breast cancer is always an indication for primary systemic treatment. Because of a lack of data from clinical trials dedicated specifically for IBC, currently the same chemotherapy regimen as in other locally advanced breast cancers is recommended. Sequential treatment with anthracyclines and taxanes is the method of choice. Response to chemotherapy should be monitored with physical examination and imaging methods (US). Radiological assessment should be carried out, when chemotherapy is completed (in some situations it can be done in the middle of treatment), and compared with baseline results. The next phase of treatment is modified radical mastectomy. Breast reconstruction is an option that can be recommended after mastectomy, but experts advise against immediate reconstruction. The treatment plan

---

ER – estrogen receptor; PgR – progesterone receptor; Ki67 – proliferation index; HER2 – human epidermal growth factor receptor 2; G – grading; CR – complete response; PR – partial response; SD – disease stabilization; PD – progressive disease; HT – hormonal therapy; ChT – chemotherapy; RT – radiotherapy; 4 × AC (60/600) – 4 cycles of doxorubicin (60 mg/m²) and cyclophosphamide (600 mg/m²); 4 × docetaxel – 4 cycles of docetaxel (100 mg/m²) every 3 weeks; 12 × P80 – 12 injections of paclitaxel (80 mg/m²) every week; BCS – breast conserving surgery

Fig. 1. The scheme of the current guidelines of neoadjuvant pharmacotherapy in patients with breast cancer
should include adjuvant radiotherapy, hormonal therapy and immunotherapy with trastuzumab if indicated.

Conclusions

According to the latest experts’ recommendations, the choice of preoperative systemic treatment should be based not only on the risk resulting from the staging but also on the predicted sensitivity of cancer cells to the therapy [55]. Figure 1 presents schematically the current guidelines of neoadjuvant pharmacotherapy in patients with breast cancer. Before starting neoadjuvant treatment, histological features of the tumor, staging and patient’s performance status should be carefully evaluated. In postmenopausal patients with high expression of hormonal receptors, HER2 negativity, Ki67 – low, lobular type and chemotherapy contraindications, endocrine treatment for breast cancer is recommended. In other patients, chemotherapy should be treated with chemotherapy plus trastuzumab. After completion of neoadjuvant treatment, the patient should undergo surgery. After the operation, proper adjuvant treatment is indicated. In the case of non-responsive or progressive disease, second line treatment should be considered.

The authors declare no conflict of interest.

References

1. Fisher B, Bryant J, Wolmark N, et al. Effect of preoperative chemotheraphy on the outcome of women with operable breast cancer. J Clin Oncol 1998; 16: 2672-85.

2. Senkus E, Kyriakides S, Pozdnyakova P, et al. A phase III randomized trial of continuous weekly doxorubicin and paclitaxel versus daily paclitaxel in neoadjuvant breast cancer. ASCO Annual Meeting 2005; 92: 147-55.

3. Cortazar P, Zhang L, Untch M, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet 2014; 384: 164-72.

4. Papi M, Sonzogni A, Moravcová M, et al. Meta-analysis of the association of breast cancer subtype and pathologic complete response to neoadjuvant chemotherapy. Eur J Cancer 2012; 48: 3342-54.

5. Kolacinska A, Blassańska-Morawiec M, Dowgier-Witczak I, Kordek R, Morawiec Z. Correlation between breast cancer receptor subtypes and nodal remission. Prz Menopauzalny 2012; 3: 174-7.

6. von Minckwitz G, Untch M, Nüesch E, et al. Impact of treatment characteristics on response of different breast cancer phenotypes: pooled analysis of the German neo-adjuvant chemotherapy trials. Breast Cancer Res Treat 2011; 125: 145-56.

7. Kuerer HM, Newman LA, Smith TL, et al. Clinical course of breast cancer patients with complete pathologic primary tumor and axillary lymph node response to doxorubicin-based neoadjuvant chemotherapy. J Clin Oncol 1999; 17: 460-9.

8. Kuerer HM, Sahin AA, Hunt KK, et al. Incidence and impact of documented eradication of breast cancer axillary lymph node metastases before surgery in patients treated with neoadjuvant chemotherapy. Ann Surg 1999; 230: 72-8.

9. Loya A, Guray M, Hennessy BT, Middleton LP, Buchholz TA, Valero V, Sahin AA. Prognostic significance of occult axillary lymph node metastases after chemotherapy-induced pathologic complete response of cytologically proven axillary lymph node metastases from breast cancer. Cancer 2009; 115: 1605-12.

10. von Minckwitz G, Kaufmann M, Kuemmel S, et al. Correlation of various pathologic complete response (pCR) definitions with long-term outcome and the prognostic value of pCR in various breast cancer subtypes: Results from the German neoadjuvant meta-analysis. J Clin Oncol 2011; 29 suppl (abstr. 1028).

11. Croshaw R, Shapiro-Wright H, Svensson E, Erb K, Julian T. Accuracy of clinical examination, digital mammogram, ultrasound, and MRI in determining postneoadjuvant pathologic tumor response in operable breast cancer patients. Ann Surg Oncol 2011; 18: 3610-3.

12. Kaufmann M, von Minckwitz G, Mamounas EP, et al. Recommendations from an international consensus conference on the current status and future of neoadjuvant systemic therapy in primary breast cancer. Ann Surg Oncol 2012; 19: 1508-16.

13. Rastogi P, Anderson SJ, Bear HD, et al. Preoperative chemotherapy: updates of National Surgical Adjuvant Breast and Bowel Project Protocols B-18 and B-27. J Clin Oncol 2008; 26: 778-85.

14. Evans TR, Yellowlees A, Foster E, et al. Phase III randomized trial of doxorubicin and docetaxel versus doxorubicin and cyclophosphamide as primary medical therapy in women with breast cancer: an anglo-celtic cooperative oncology group study. J Clin Oncol 2005; 23: 2988-95.

15. von Minckwitz G, Raab G, Caputo A, et al. Doxorubicin with cyclophosphamide followed by docetaxel every 21 days compared with doxorubicin and docetaxel every 14 days as preoperative treatment in operable breast cancer: the GEPARTRIO study of the German Breast Group. J Clin Oncol 2005; 23: 2676-85.

16. Untch M, Konecny G, Ditsch N, et al. Dose-dense sequential epirubicin-paclitaxel as preoperative treatment of breast cancer: results of a randomised AGO study. Proc Am Soc Clin Oncol 2002; 21 (abstr. 133).

17. Green MC, Buzzard AJ, Smith T, et al. Weekly paclitaxel improves pathologic complete remission in operable breast cancer when compared with paclitaxel once every 3 weeks. J Clin Oncol 2005; 23: 5983-92.

18. von Minckwitz G, Sinn HP, Raab G, et al. Clinical response after two cycles compared to HER2, Ki-67, p53, and bcl-2 in independently predicting a pathological complete response after preoperative chemotherapy in patients with operable carcinoma of the breast. Breast Cancer Res 2008; 10: R30.

19. Zhou B, Yang DQ, Xie F. Biological markers as predictive factors of response to neoadjuvant taxanes and anthracycline chemotheraphy in breast carcinoma. Chin Med J (Engl) 2008; 121: 387-91.

20. Sikov WM, Dizon DS, Stenger R, et al. Frequent pathological complete responses in aggressive stages II to III breast cancers with every-4-week carboplatin and weekly paclitaxel with or without trastuzumab: a Brown University Oncology Group Study. J Clin Oncol 2009; 27: 4693-700.

21. Prisack HB, Karreman C, Modlich O, Audretsch W, Danae M, Rezali M, Bojar H. Predictive biological markers for response of invasive breast cancer to anthracycline/cyclophosphamide-based primary (radio-)chemotherapy. Anticancer Res 2005; 25: 4615-21.

22. Rody A, Karl T, Gätje R, et al. Gene expression profiling of breast cancer patients treated with docetaxel, doxorubicin, and cyclophosphamide within the GEPARTRIO trial: HER-2, but not topoisomerase II alpha and microtubule-associated protein tau, is highly predictive of tumor response. Breast 2007; 16: 86-93.

23. Burcombe RI, Makris A, Richman PJ, et al. Evaluation of ER, PgR, HER-2 and Ki-67 as predictors of response to neoadjuvant anthracycline chemotherapy for operable breast cancer. Br J Cancer 2005; 92: 147-55.

24. Sorialie T, Tishbirani R, Parker J, et al. Repeated observation of breast tumor subtypes in independent gene expression data sets. Proc Natl Acad Sci U S A 2005; 102: 8418-23.

25. Rouzier R, Perou CM, Symmans WF, et al. Breast cancer molecular subtypes respond differently to preoperative chemotherapy. Clin Cancer Res 2005; 11: 5678-85.

26. Parker J, Prat A, Cheang M, Lenburg ME, Paik S, Perou C. Breast cancer molecular subtypes predict response to anthracycline/taxane-based chemotherapy. SABCS, 2009. http://www.abstracts-2view.com/sabcs09/view.php?mu=p2010.

27. Chang H, Glasy J, Allison MA, Kass FC, Elashoff R, Chung DU, Gornbein J. Differential response of triple-negative breast cancer
The role of preoperative systemic treatment in patients with breast cancer

47. Cataliotti L, Buzdar AU, Noguchi S, Bines J, Takatsuka Y, Petrakos A, Smith IE, Dowsett M, Ebbs SR, et al. Neoadjuvant treatment of postmenopausal breast cancer in elderly women: the Pre-Operative "Arimidex" Compared to Tamoxifen (PROACT) trial. J Clin Oncol 2004; 22: 3739-46.

48. Ellis MJ, Ma C. Letrozole in the neoadjuvant setting: the PO24 trial. Breast Cancer Res Treat 2007; 105: 33-43.

49. Eiermann W, Paepeke S, Appelstaedt J, et al. Preoperative treatment of postmenopausal breast cancer patients with letrozole: A randomized double-blind multicenter study. Ann Oncol 2001; 12: 1527-32.

50. Mustacchi G, Mansutti M, Sacco C, Banni S, Farris A, Cazzaniga M, Cozzi M, Dellach C. Neo-adjuvant exemestane in elderly patients with breast cancer: a phase II, multicentre, open-label, Italian study. Ann Oncol 2009; 20: 655-9.

51. Alba E, Calvo L, Albaneli J, et al. Chemotherapy (CT) and hormone-therapy (HT) as neoadjuvant treatment in luminal breast cancer patients: results from the GEICAM/2006-03, a multicenter, randomized, phase-II study. Ann Oncol 2012; 23: 3069-74.

52. Ellis MJ, Suman VJ, Hoog J, et al. Randomized phase II neoadjuvant comparison between letrozole, anastrozole, and exemestane for postmenopausal women with estrogen receptor-rich stage 2 to 3 breast cancer: clinical and biomarker outcomes and predictive value of the baseline PAM50-based intrinsic subtype – ACOSOG Z1031. J Clin Oncol 2011; 29: 2342-9.

53. Ellis MJ, Tao Y, Luo J, et al. Outcome prediction for estrogen receptor-positive breast cancer based on postneoadjuvant endocrine therapy tumor characteristics. J Natl Cancer Inst 2008; 100: 1380-8.

54. Dawson S, Merajver SD, Viens P, et al. International expert panel on inflammatory breast cancer: consensus statement for standardized diagnosis and treatment. Ann Oncol 2011; 22: S15-23.

55. Goldhirsch A, Wood WC, Coates AS, Gelber RD, Thürlimann B, Senn HJ; Panel members. Strategies for subtypes-dealing with the diversity of breast cancer: highlights of the St. Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2011. Ann Oncol 2011; 22: 1736-47.

Address for correspondence
Sylwia Dębiska-Szmich PhD
Department of Chemotherapy
Chair of Oncology
Medical University of Lodz, Poland
e-mail: sylwia.debska@o2.pl

Submitted: 07.08.2013
Accepted: 29.05.2014