The role of preoperative systemic treatment in patients with breast cancer

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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.

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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 T3N1). 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 (T3N0-1).

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 eradicated 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 histopathologic 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 agressive 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 increased number of cycles was more pronounced in hormone receptor-positive tumors (OR 1.35) than in HR-negative tumors (OR 1.04; p = 0.046) and with higher anthracycline dose in HER2-negative tumors (OR 1.61), compared to HER2-positive tumors (OR 0.83; p = 0.14). Adding trastuzumab to neoadjuvant chemotherapy in HER2-positive tumors increased the odds of pCR 3.2-fold ($p < 0.001$). However, there was no evidence for an 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 [13]	*N* = 2411 AC 4× AC 4x → T 4×	AC – 13% vs. AC → T – 26% $p < 0.0001$
GEPARDUO von Minckwitz 2005 [15]	*N* = 913 AT q2w 4× AC q3w 4× → T q3w 4×	AT – 7% vs. AC → T – 14.3% $p < 0.001$
AGO Untch 2002 [16]	*N* = 475 E q2w 3x → P q2w 3× EP q3w 4×	E → P – 18% vs. EP – 10% $p = 0.03$
Green 2005 [17]	*N* = 258 P q1w 12× → FAC 4× P q3w 4× → FAC 4×	P q1w – 28.2% vs. P q3w – 15.7% $p = 0.02$

AC – doxorubicin + cyclophosphamide; T – docetaxel; pCR – complete pathologic response; AT – doxorubicin + docetaxel; E – epirubicin; P – paclitaxel; EP – epirubicin + paclitaxel; q1w – given every 1 week; q3w – given every 3 weeks; FAC – fluorouracil + doxorubicin + cyclophosphamide

Table 2. Examples of studies exploring effectiveness of preoperative chemotherapy in patients with different breast cancer subtypes distinguished by either genetic or immunohistochemical classification

Study	Method of subtype identification	Treatment (*N* – number of patients)	Results – pCR rate	
Rouzier *et al*. 2005 [25]	Genotyping Affymetrix U133A	*N* = 82 Paclitaxel → FAC	Luminal A/B HER2+ Basal	7% 45% 45%
Parker *et al*. 2009 [26]	Genotyping PAM50	*N* = 347 anthracycline + taxane	Luminal A Luminal B Her2+ Basal	7% 17% 36% 43%
Chang *et al*. 2010 [27]	IHC	*N* = 74 Carboplatin (AUC 6) + taxane ± trastuzumab	HR+/HER2– HER2+trast+ HER2+trast– TNBC	19.4% 40% 7.1% 54.6%
Fasching *et al*. 2011 [31]	IHC	*N* = 547 Anthracycline/ anthracycline + taxane/other ± trastuzumab	HR + HER2– Ki67 < 38% HR + HER2– Ki67 > 38% HR ± HER2+trast+ HR ± HER2+trast– TNBC	3% 18.9% 52% 28.8% 47.3%
Straver *et al*. 2010 [28]	IHC	*N* = 254 AC/AT/paclitaxel + trastuzumab + carboplatin	HR + HER2– HER2+trast+ HER2+trast– TNBC	2% 35% 8% 28%

IHC – immunohistochemistry, TNBC – triple-negative breast cancer, trast+ – patients treated preoperatively with trastuzumab, trast– – patients not treated preoperatively with trastuzumab

- Luminal A: ER+, PR+, HER2–, Ki67 – low[1] and PR – high[2],
- Luminal B: ER+, PR+, HER2–, Ki67 – high or PR – low,
- Luminal HER2+: ER+, PR+, HER2+, any Ki67,
- HER2-positive: ER–, PR–, HER2+, any Ki67,
- Basal (TNBC): ER–, PR–, HER2–, any Ki67.

Table 2 presents examples of research exploring the effectiveness of preoperative chemotherapy in patients with different breast cancer subtypes based on either genetic or immunohistochemical classification [25–29]. These papers show that pCR is rarely achieved in patients with luminal A subtype (3–7%), but it is significantly more often seen in patients with TNBC or HER2-positive breast cancer. The results of a study by Kołacińska *et al.* [5] are in agreement with these observations. The rate of axillary pCR was significantly higher in TNBC patients compared with ER(+) PR(+) HER2(–) patients and ER(+)PR(+)HER2(+) ones [5]. As mentioned before, in HER2-positive tumors the pCR rate may be higher if an anti-HER2 agent (e.g. trastuzumab) is given with preoperative chemotherapy.

The study by Straver *et al.* [28] indicated that the response to preoperative chemotherapy depended on immunohistochemical subtype, but it also underlined the predictive value of histological subtype of breast cancer. The pCR rate in patients with lobular cancer was only 2%, whereas in patients with ductal cancer it was 12%. This observation is not surprising, as most lobular cancers are categorized in luminal A subtype [29].

The fact that breast cancer subtype can be predictive for achieving pCR 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,

[1]Ki67 expression should be interpreted according to local laboratory values, suggested cut-off value is a median Ki67 score in receptor-positive disease
[2]Suggested cut-off value for PR expression is 20%

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 GeparSixto 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 [33]	FAC/FEC/AC T + FAC/T + FEC Taxane monotherapy	70 125 17	20 28 12
Carey *et al*. 2007 [34]	AC	34	27
Wang *et al*. 2009 [35]	AT	21	38
Sikov *et al*. 2009 [20]	Carboplatin (AUC 6) + paclitaxel	12	67
Chang *et al*. 2010 [27]	Carboplatin (AUC 6) + docetaxel	11	54.6
Silver *et al*. 2010 [36]	Cisplatin	28	22

AC – doxorubicin + cyclophosphamide, T – docetaxel, pCR – complete pathologic response, AT – doxorubicin + docetaxel, FAC – fluorouracil + doxorubicin + cyclophosphamide, fluorouracil + 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	
			BRCA1+	BRCA2+
Byrski *et al*. 2009 [37]	Cisplatin	10	9/10	
Hubert *et al*. 2009 [38]	Anthracycline-based chemotherapy	15	2/15	
Arun *et al*. 2011 [39] Retrospective	AT Anthracycline-based chemotherapy	64 14	21/46 (0.46) 4/9 (0.44)	3/18 (0.17) 0/5
Byrski *et al*. 2009 [40] Retrospective	CMF AT AC/FAC Cisplatin	14 25 51 12	1/14 2/25 11/51 (0.22) 10/12 (0.83)	
Chappuis *et al*. 2002 [43] Retrospective	Anthracycline-based chemotherapy	9	4/9	

CMF – cyclophosphamide, methotrexate, fluorouracil, AC – doxorubicin + cyclophosphamide, AT – doxorubicin + docetaxel, FAC – fluorouracil + doxorubicin + cyclophosphamide

Table 5. Examples of studies exploring effectiveness of preoperative hormonal therapy in patients with breast cancer

Study	Treatment (*N*, *n* – number of patients)	Results
Bergman *et al*. 1995 [44]	*N* = 85, TAM, age > 75 years, unknown HR expression	CR = 14.1%, PR = 23.5%
Bradbeer *et al*. 1983 [45]	*N* = 161, age > 70 years, TAM	ORR = 61%, CR = 27%
IMPACT Smith *et al*. 2005 [46]	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
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 6 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., Allred score 6–8 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%

HR – hormonal 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 four 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 was a very rare phenomenon and it was not related to outcome. The surrogates of treatment effectiveness were objective response (OR) and improvement of feasible surgery. OR was calculated as the percentage of patients with a clinical complete response (CR) or partial response (PR). The largest diameters of the tumors were measured by ultrasound and/or caliper and/or mammography at baseline and at the completion of neoadjuvant treatment. Endocrine therapy produced a 20–79% objective response rate according to different authors. The PROACT, P024 and Eiermann *et al.* studies revealed that treatment with aromatase inhibitors (IA) was more effective than with tamoxifen in postmenopausal patients [47–49]. Preoperative hormone therapy should be continued for 3–4 months. According to Mustacchi *et al.* [50], prolonged treatment produced a higher response rate.

Still there are only a few studies comparing the value of preoperative chemotherapy and hormonal therapy in patients with luminal A breast cancer, and usually they are dedicated to postmenopausal patients. These patients seem to have little benefit from chemotherapy, and hormonal treatment seems to be a valuable method. Postmenopausal and premenopausal patients with operable luminal (ER+/PR+/HER2–/CK8/18+) breast cancer were eligible for the GEICAM/2006-03 study [51]. Forty seven patients were treated with neoadjuvant chemotherapy (4 cycles of epirubicin and cyclophosphamide, then 4 cycles of docetaxel), whereas hormonal therapy with exemestane was administered to 48 patients for 24 weeks (in premenopausal patients it was combined with goserelin). It appeared that patients with Ki67 expression higher than 10% had a higher objective response rate if they were treated with chemotherapy compared with hormonal therapy. However, in patients with Ki67 < 10% both methods were equivalent and hormonal treatment was less toxic. This study proved that preoperative hormonal therapy is of value in patients with luminal A breast cancer.

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,

53] 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 P024 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

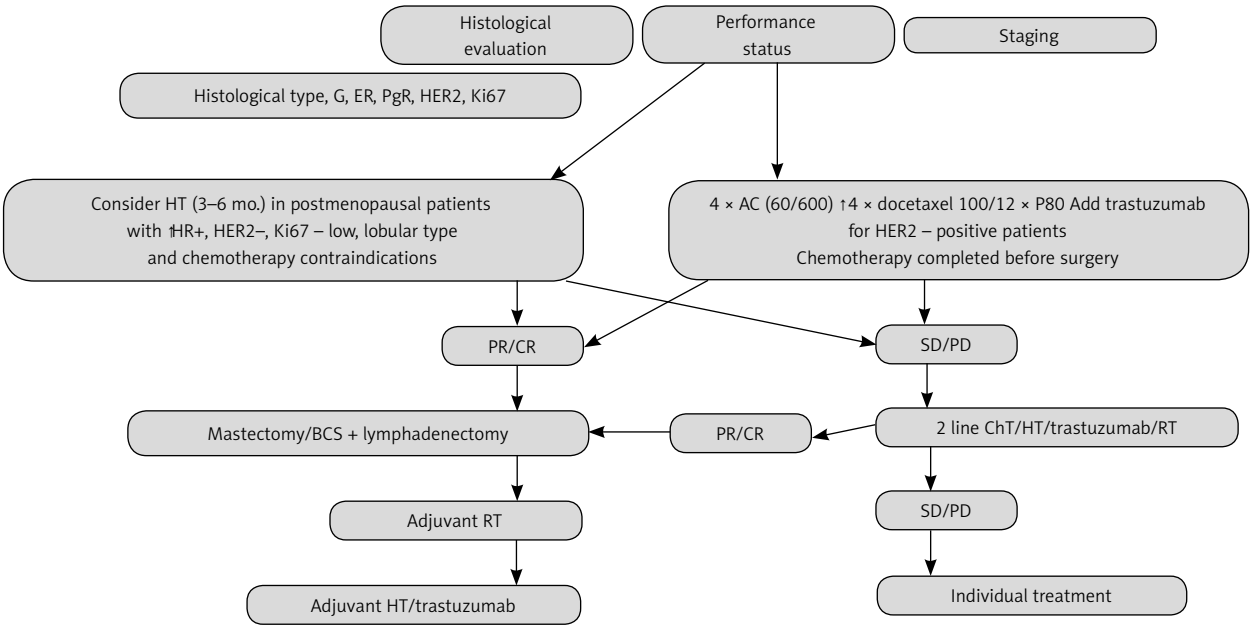
Inflammatory breast cancer (IBC) is an indication for primary systemic treatment because skin involvement is categorized as T4. According to current guidelines [54] to diagnose inflammatory breast cancer the following criteria should be met:

- 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 injection 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 3–6 months is strongly endorsed. In other patients, chemotherapy with a sequential regimen of anthracyclines and taxanes is recommended. Patients with HER2-positive disease 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.

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