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REVIEW ARTICLE

Piotr J Wysocki[1], **Maciej Krzakowski**[2]

[1]Department of Oncology, Jagiellonian University *Collegium Medicum*, Kraków, Poland
[2]Department of Lung Cancer and Chest Tumours, Maria Skłodowska-Curie National Research Institute of Oncology, Warsaw, Poland

Preoperative treatment of HER2-positive breast cancer

Address for correspondence:
Prof. dr hab. n. med. Piotr Wysocki
Klinika Onkologii,
Uniwersytet Jagielloński
— *Collegium Medicum*, Kraków
e-mail: piotr.wysocki@uj.edu.pl

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ABSTRACT

Preoperative chemotherapy is more and more frequently used in the treatment of localized and locally-advanced breast cancer. This approach not only creates optimal conditions for organ-sparing surgery but also provides us with valuable information on the biology and chemosensitivity of cancer. This data is then crucial for the choice of systemic adjuvant therapy. The availability of two anti-HER2 targeted agents (pertuzumab and trastuzumab) for the neoadjuvant treatment of breast cancer significantly improves the efficacy of this approach. Significantly increased percentage of patients experiencing complete pathological response correlates with improved outcomes. This article is aimed at summarizing current knowledge regarding the role of pertuzumab in neoadjuvant treatment of HER2-positive breast cancer and comprises essential guidelines for the optimal use of currently reimbursed therapies in this disease.

Key words: neoadjuvant treatment, preoperative chemotherapy, HER2-positive, pertuzumab, trastuzumab, breast cancer

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Introduction

After a long waiting period, on September 1, 2019 the Ministry of Health issued a positive decision regarding reimbursement of pertuzumab in the preoperative treatment of patients with locally advanced HER2-positive breast cancer. The changes introduced into the drug program allow not only optimisation of safety but they also increase the effectiveness of neoadjuvant treatment. In contrast to the provisions of the drug program for palliative treatment of patients with HER2-positive breast cancer, which, based on the results of CLEOPATRA study [1] strictly defined treatment regimen based on the combination of pertuzumab and trastuzumab, in preoperative management various treatment regimens including these drugs can be used. Expanding treatment options with new regimens is always, especially in the first period, associated with many doubts about the optimal combination of drugs, taking into account their safety and effectiveness. This article summarises the current knowledge regarding the use of trastuzumab and pertuzumab in preoperative treatment, with particular emphasis on the possibility of using this drug in clinical practice in Poland.

The role of preoperative treatment

Preoperative treatment is one of the options for the management of patients with early breast cancer. Despite a number of studies comparing the benefits of neoadjuvant versus adjuvant therapy, the advantage of preoperative treatment in relation to patient prognosis has not been demonstrated. The main goal of neoadjuvant treatment is to increase the feasibility of surgical treatment in patients with initially inoperable, locally advanced tumour (IIIA–C and "inflammatory" breast cancer), in whom resection is impossible, or to create the possibility of breast-conserving surgery (BCS) in the case of primary operable tumours (T2 N0–1 M0). Preoperative chemotherapy allows an increase in the percentage of BSC procedures from a few to several per cent; however, in many patients, regardless of the response to systemic treatment, such a procedure cannot

be used due to the presence of objective contraindications. A recent meta-analysis comparing preoperative and postoperative treatment did not show differences according primary prognostic parameters. However, this analysis showed a significantly increased percentage of local recurrences in patients receiving preoperative treatment, which resulted from a much higher percentage of BCS procedures compared to patients who were undergoing primary surgical treatment [2].

Very important additional benefits associated with preoperative chemotherapy include early application of systemic treatment and obtaining information about the anti-tumour effect of the neoadjuvant treatment based on postoperative material examination. Confirmation of residual disease after preoperative treatment is an indication to consider adjuvant treatment with another cytotoxic drug (capecitabine in HER2-negative cancers or T-DM1 in HER2-positive cancers).

Pathological complete response

In modern clinical trials assessing different strategies of preoperative chemotherapy, the pathological complete response (pCR) rate is the most commonly used primary endpoint. Unfortunately, for years, this parameter was not standardised, and in many studies, different research groups defined it differently; in some studies only the breast tumour was assessed, in others lymph nodes were also included, and sometimes pCR could be found even if carcinoma in situ or single invasive cancer lesions were present [2]. The discrepancies in pCR definition between different studies make it very difficult to compare individual preoperative treatment strategies and perform meta-analyses that could clearly indicate the optimal neoadjuvant chemotherapy regimen.

However, there is no doubt that the effectiveness of preoperative treatment depends primarily on the histological type of breast cancer. The expression of steroid receptors and a low proliferative index correlate with a lower probability of obtaining pCR (6.4% *vs.* 31% for luminal subtype A and the so-called "triple negative" cancer, respectively) [3]. Based on, among other things, the combined analysis of the German Breast Group (GBG) studies, it is known that patients achieving a complete pathological response (ypT0 ypN0) after preoperative chemotherapy have a very good prognosis regarding disease-free survival (DFS, HR = 4.04; $P < 0.001$) and overall survival (OS, HR = 7.39; $P < 0.001$). In the case of HER2-positive breast cancer, the probability of pCR depends on the use of molecularly targeted therapies. In the mentioned GBG analysis the pCR rate after the use of pre-operative chemotherapy in patients with luminal B HER2-negative and HER2-positive breast cancer was about 11%, while the combination of chemotherapy and trastuzumab doubled this percentage (to 22%). For HER2-positive, oestrogen receptor-negative (OR-negative) and progesterone receptor-negative (PR-negative) cancer, the pCR rates were 28% and 33% for chemotherapy and combination chemotherapy with trastuzumab, respectively [3]. A meta-analysis involving more than 11,000 breast cancer patients undergoing neoadjuvant treatment showed a significantly increased pCR rate after chemotherapy with trastuzumab (31–50%) compared to chemotherapy alone (18–30%) in the HER2-positive breast cancer population [4]. Furthermore, this study showed a strong relationship between pCR and prognosis in patients with HER2-positive/ER-negative/PR-negative breast cancer receiving trastuzumab in neoadjuvant therapy (EFS, HR = 0.15, 95% CI 0.09–0.27; OS, HR = 0.08, 95% CI 0.03–0.22).

Preoperative treatment of HER2-positive breast cancer

HER2 receptor overexpressed in breast cancer cells is one of the key mechanisms responsible for the high aggressiveness of the cancer, while being a critical therapeutic target. In 1998, trastuzumab (a monoclonal antibody that binds and inactivates HER2 receptor) was registered in the treatment of patients with metastatic breast cancer, and in 2006 the registered indications were expanded to include adjuvant treatment based on studies that showed a significant improvement of prognosis [5–7].

More than nine years ago, the first evidence regarding the efficacy and safety of preoperative chemotherapy combined with trastuzumab in patients with HER2-positive breast cancer was reported. Since then, several subsequent clinical trials have been conducted assessing various neoadjuvant chemotherapy regimens with trastuzumab. In the following years, with the advent of new anti-HER2 drugs active in generalised HER2-positive breast cancer (pertuzumab and lapatinib), assessment of the possibility of combining these drugs within neoadjuvant treatment was also started. The purpose of the combination of anti-HER2 drugs was to increase the likelihood of a response and improve safety (primarily to reduce the risk of cardiotoxicity) by reducing the intensity of chemotherapy included in preoperative treatment [8–11]. Table 1 summarises the studies assessing preoperative regimens containing anti-HER2 antibodies.

Combination of anti-HER2 drugs with anthracyclines

In some studies assessing the role of trastuzumab in preoperative treatment, it was used concomitantly

Table 1. Summary of clinical studies evaluating trastuzumab in neoadjuvant treatment. P — paclitaxel, T — trastuzumab, A — doxorubicin, C — cyclophosphamide, D — docetaxel (D75 — 75 mg/m^2 q3w, D100 — 100 mg/m^2 q3w, D75/100 — dose escalation possible), E — epirubicin, F — 5-fluorouracil, K — carboplatin, M — methotrexate, PER — pertuzumab

Study	Number of patients	Regimen	pCR	Ref.
MDACC	23	4 × P + T → 4 × FEC + T	65%	[12]
NOAH	117	3 × AP + T → 3 × P + T → 3 × CMF + T	38%	[11]
NeoALLTO	149	T → T + 12 × P	28%	[13]
HannaH	299	4 × D75 + T → 4 × FEC + T	34%	[14]
GeparQuinto	309	4 × EC + T → 4 × D100 + T	30%	[15]
ACOSOG Z1041	140	4 × FEC → 12 × P + T	48%	[16]
	142	12 × P + T → 4 × FEC + T	47%	
NSABP B-41	181	4 × AC → 4 × P + T	49%	[7]
REMAGUS 2	62	4 × EC → 4 × D100 + T	26%	[17]
GEICAM/2006-14	50	4 × EC → 4 × D100 + T	48%	[18]
CHER-LOB	36	12 × P + T → 4 × FEC + T	25%	[19]
PCH	29	12 × P + K + T	69%	[20]
NeoSphere	107	4 × D(75/100) + T	29%	[10]
	107	4 × D(75/100) + PER + T	46%	
	107	4 × PER + T	17%	
	96	4 × D(75/100) + PER	24%	
TRYPHAENA	72	3 × FEC + PER + T → 3 × DXL(75/100) + PER + T	61%	[11]
	75	3 × FEC → 3 × DXL(75/100) + PER + T	57%	
	76	6 × D75 + K + T + PER (TCHP)	66%	
KRISTINE	221	6 × D75 + K + T + PER (TCHP)	56%	[21]
	223	T-DM1 + PER	44%	

with anthracyclines, although this combination is associated with a high risk of myocardial insufficiency and is generally not recommended for adjuvant and palliative treatment. Despite this, in several studies (e.g. NOAH, GeparQuinto, ACOSOG Z1041, HannaH, or Cher-Lob) in which trastuzumab was associated with anthracycline-containing regimens (a total of over 1000 patients), no clinically significant increase of cardiotoxicity risk was observed [14, 16, 19, 22]. There is no doubt, however, that patients participating in these trials were subject to very close cardiological monitoring, which is not a standard in routine clinical practice. Therefore, the use of preoperative chemotherapy regimens combining trastuzumab with anthracyclines is not recommended.

One of the reasons for combining anthracyclines with trastuzumab as part of preoperative treatment was an attempt to increase the effectiveness of classic neoadjuvant chemotherapy regimens, usually based on anthracyclines and taxoids. According to assumptions, concomitant use of trastuzumab with all cycles of preoperative chemotherapy should have been more effective than using this drug only during taxoid administration. However, the majority of studies on preoperative treatment of HER2-positive breast cancer patients did not allow conclusions to be drawn about the real benefits of concurrent use of trastuzumab and anthracyclines, because they did not compare two trastuzumab administration regimens in parallel. In the phase III ACOSOG Z1041 study, 282 patients with initially operable HER2-positive breast cancer were randomly assigned (1:1) to a sequential arm receiving the 4 × FEC → 12 × PXL 80 mg/m^2 + trastuzumab or to a concurrent arm with the regimen 12 × PXL + trastuzumab → 4 × FEC. No significant difference was seen in pCR rate (primary endpoint) between study arms; pCR was reported in 56.5% of patients in the sequential arm and 54.2% in the concurrent arm (OR = 0.90; 95% CI 0.55–1.49). The deterioration of left ventricular function (G1–4 and G3–4 according to WHO CTC) was observed in 3.6% and 0% of patients in the sequential arm and 8.4% and 0.7% in the concurrent arm, respectively [14]. The three-arm, phase II TRYPHAENA study compared in two arms concurrent or sequential use of FEC regimen with the combination of pertu-

zumab and trastuzumab (FEC + trastuzumab + pertuzumab → docetaxel + trastuzumab + pertuzumab *vs.* FEC → docetaxel + trastuzumab + pertuzumab) [11]. In this study, pCR rates were 51% in the concurrent arm and 45% in the sequential arm, but the risk of neutropaenic fever was clearly higher in the concurrent arm than in the sequential arm (18% *vs.* 9%) with comparable cardiotoxicity.

Optimal combination of pertuzumab with trastuzumab and chemotherapy in preoperative treatment

Compared to the number of clinical studies on the role of trastuzumab in the preoperative treatment of patients with HER2-positive breast cancer, the number of studies on the combination of trastuzumab with pertuzumab is significantly smaller. Many early studies on trastuzumab focused on the potential for reducing the intensity of chemotherapy by excluding anthracyclines. A study conducted by Hurley et al. involved 48 patients with locally advanced or inflammatory HER2-positive breast cancer. Preoperative treatment administered for 12 weeks (docetaxel 70 mg/m^2 d. 1 + cisplatin 70 mg/m^2 d. 1 + weekly trastuzumab — four courses in total) led to a pathological complete response in 23% of patients [23]. Another study looked at the activity of combination of carboplatin at a dose of AUC6 + paclitaxel 80 mg/m^2 and trastuzumab at a weekly dose during 12 weeks of preoperative treatment in patients with operable (majority of patients) HER2-positive breast cancer. Pathological complete responses were observed in a surprisingly high percentage of patients (76%), which could be a consequence of enrolment of patients with small tumours [20]. In another phase II study of neoadjuvant chemotherapy without anthracycline, 56 patients with HER2-positive breast cancer (IIB–IIIC) were randomly assigned to two preoperative chemotherapy regimens based on the combination of trastuzumab, carboplatin, and paclitaxel (PXL 175 mg/m^2 + carboplatin AUC6 + trastuzumab in a three-week schedule — a total of four courses or PXL 80 mg/m^2 d. 1, 8, 15 + carboplatin AUC2 d. 1, 8, 15 + trastuzumab on a weekly basis — four courses in total). In the weekly chemotherapy arm a significant increase of pCR rate, from 40.7% to 69% (HR = 0.3; 95% CI 0.1–0.9), was observed, which was particularly marked in patients with hormone-dependent and HER2-positive breast cancer — 67% *vs.* 21% (71% *vs.* 62% in ER-negative/PR-negative tumours) [24]. The percentage of side effects was similar in both arms.

A key study on the role of pertuzumab in preoperative treatment (phase II NeoSphere study) [10] even allowed for complete abandonment of chemotherapy before surgery. In this study, 417 HER2-positive breast cancer patients were randomly assigned to preoperative treatment according to the schedules — (i) 4 × docetaxel + trastuzumab, (ii) 4 × docetaxel + trastuzumab + pertuzumab, (iii) 4 × trastuzumab + pertuzumab, and (iv) 4 × docetaxel + pertuzumab. After surgery, all patients received anthracycline-based adjuvant therapy with trastuzumab for up to 12 months, and patients in the non-chemotherapy arm also received docetaxel. The NeoSphere study showed the highest pCR rate in the arm receiving a three-drug regimen (docetaxel + trastuzumab + pertuzumab) — 46%, compared to 29% (docetaxel + trastuzumab), 24% (docetaxel + pertuzumab), and 17% (pertuzumab + trastuzumab). This study also showed no additional toxicity associated with the addition of pertuzumab.

In the aforementioned TRYPHAENA study, in addition to anthracycline-containing regimens, the efficacy and safety of a docetaxel, carboplatin, and trastuzumab with pertuzumab regimen (TCHP) were also assessed. In this arm, a very high pCR rate of 64% was achieved at the expense of side effects such as febrile neutropaenia (17% of patients), G3 diarrhoea (12%), G3 anaemia (17%), and thrombocytopaenia (12%).

In the phase III KRISTINE study comparing the experimental regimen with trastuzumab emtansine (T-DM1) and pertuzumab *versus* TCHP in preoperative treatment, a high pCR rate of 55.7% was confirmed in the TCHP arm (221 patients) *versus* 44.4% in the experimental arm [21].

Regimens of preoperative chemotherapy in HER2-positive breast cancer

Trastuzumab *s.c.* — 600 mg *s.c.*; dosing every three weeks
Trastuzumab *i.v.* — 8 mg/kg (first loading dose) then 6 mg/kg *i.v.*; dosing every three weeks
Pertuzumab — 840 mg *i.v.* (loading dose followed by 420 mg *i.v.*) — every 3 week

AC → PTP
Four cycles — doxorubicin 60 mg/m^2 *i.v.* + cyclophosphamide 600 mg/m^2 *i.v.* d. 1 every three weeks, then paclitaxel 80 mg/m^2 *i.v.* d. 1 weekly for 12 weeks + trastuzumab* + pertuzumab**
After surgery trastuzumab should be continued for up to a year.

AC → DTP
Four cycles — doxorubicin 60 mg/m^2 *i.v.* + cyclophosphamide 600 mg/m^2 *i.v.* d. 1 every three weeks, then four cycles — docetaxel 100 mg/m^{2*} *i.v.* d. 1 every three weeks + trastuzumab* + pertuzumab**

After surgery trastuzumab should be continued for up to a year.

EC → DTP
Four cycles — epirubicin 90 mg/m^2 *i.v.* + cyclophosphamide 600 mg/m^2 *i.v.* d. 1 every three weeks, then
four cycles — docetaxel 100 mg/m^{2*} *i.v.* d. 1 every three weeks + trastuzumab*+ pertuzumab**
After surgery trastuzumab should be continued for up to a year.

EC → PTP
Epirubicin 75 mg/m^2 *i.v.* + cyclophosphamide 500 mg/m^2 *i.v.* d. 1 every three weeks, then
paclitaxel 80 mg/m^2 *i.v.* weekly for 12 weeks + trastuzumab* + pertuzumab**
After surgery trastuzumab should be continued for up to a year.

TCHP
Six cycles — docetaxel 75 mg/m^2 *i.v.* + carboplatin AUC6 *i.v.* + trastuzumab* + pertuzumab**
After surgery trastuzumab should be continued for up to a year.

PCHP
Four cycles — paclitaxel 80 mg/m^2 *i.v.* d. 1, 8, 15 + carboplatin AUC2 *i.v.* d. 1, 8, 15, concomitantly trastuzumab* + pertuzumab**
After surgery trastuzumab should be continued for up to a year.

Summary

The introduction of anti-HER2 drugs significantly improved the effectiveness of neoadjuvant treatment in HER2-positive breast cancer patients. Without a significant increase in toxicity, it was possible to achieve a significant increase in pCR rate and increase the percentage of patients undergoing breast-conserving surgery. The current changes in the "Breast Cancer Treatment" drug program finally allow us to offer patients with HER2-positive breast cancer effective and safe preoperative treatment in line with international standards in the case of local advancement (N+) or planned breast-conserving surgery in patients with a tumour of diameter > 2 cm. When applying preoperative treatment in patients with HER2-positive breast cancer, it should be remembered that the use of trastuzumab is not the only condition for obtaining the expected clinical benefits. The maximum effectiveness of neoadjuvant treatment is guaranteed by the use of an optimal combination of chemotherapy with anti-HER2 drugs and the maintenance of the originally planned dose intensity. It should also be remembered that the combination of trastuzumab and pertuzumab with docetaxel monotherapy (as in the NeoSphere study) is not a recommended preoperative treatment because of the need for use of anthracycline-containing adjuvant chemotherapy. The use of only the docetaxel + trastuzumab + pertuzumab combination not only reduces the likelihood of obtaining pCR, but also precludes or significantly delays postoperative use of trastuzumab. If there is any doubt about the tolerability of the planned treatment, alternative chemotherapy regimens (e.g. with lower cardiotoxic potential — anthracycline-free regimens) or showing a lower risk of myelosuppression (weekly regimens) should be considered. As in the case of adjuvant treatment, unjustified dose reductions of cytotoxic drugs (e.g. in obese patients [12]) are unfavourable in terms of the probability of response and patient prognosis, and they should be considered primarily if unacceptable tolerance of treatment occurs.

*Trastuzumab — [intravenous formulation] 8 mg/kg *i.v.* (loading dose) followed by 6 mg/kg *i.v.* — every 3 weeks; [subcutaneous formulation] — 600 mg *s.c.* — every 3 weeks

**Pertuzumab — 840 mg/kg *i.v.* (loading dose) followed by 420 mg/kg *i.v.* — every 3 weeks

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