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REVIEW ARTICLE

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Practical aspects of pertuzumab treatment in patients with breast cancer — management of the most common adverse events

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ABSTRACT

Treatment outcomes of patients diagnosed with breast cancer with overexpression of the HER2 receptor have been significantly improved by the use of pertuzumab. Its use, however, is associated with the occurrence of various, more or less severe, adverse events. Some of them had already been observed in clinical practice during treatment with another monoclonal antibody directed against the HER2 receptor, trastuzumab. New toxicities, which occurred in a higher grade or significantly more frequently during treatment with pertuzumab are diarrhoea, neutropaenia and febrile neutropaenia, and skin toxicities. Their severity is generally acceptable, and proper management in the case of their occurrence is crucial for optimal causal treatment. This paper proposes schemes for management of the most common adverse events during the use of pertuzumab.

Key words: pertuzumab, breast cancer, HER2, toxicity

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Pertuzumab — mechanism of action and effectiveness

Pertuzumab is a humanised IgG1-class monoclonal antibody directed against subdomain 2 of the extracellular human epidermal growth factor receptor (HER2) dimerization domain [1]. HER2 receptor, due to its constitutive ligand-independent dimerisation, has an ease of creating of homo- and heterodimers in overexpression state. The main mechanism of HER2 receptor activity in the cell is associated with its heterodimerisation, and the HER2/HER3 heterodimer is the most potent signal transmitter. Trastuzumab blocks the subdomain IV of the extracellular domain of HER2 primarily inhibiting signalling and inducing antibody-dependent cellular cytotoxicity (ADCC). Pertuzumab, by binding to the HER2 domain, blocks HER2 heterodimerisation with other activated, relevant ligands in the HER family, including EGFR, HER3, and HER4. This drug, like trastuzumab, also induces ADCC. As a result, the combination of trastuzumab and pertuzumab synergistically inhibits intracellular signalling pathways — mitogen-activated kinase pathway (MAPK) and PI3K-AKT-mTOR pathway [1, 2]. This results in the inhibition of cell growth and apoptosis.

Research in the field of molecular biology has shown that one of the causes of resistance to trastuzumab is heterodimerisation of HER2 with HER3 receptor [3]. Because pertuzumab inhibits this dimerisation, it was assumed that this drug may play a role in the breakdown of trastuzumab resistance. The efficacy of pertuzumab in the treatment of breast cancer has been confirmed in several clinical trials, and the randomised phase III CLEOPATRA study was the basis for drug registration in this indication [4]. 808 patients with metastatic or locally advanced inoperable breast cancer were included in

this study. As a result of randomisation, patients were assigned to trastuzumab, docetaxel, and placebo (control) or pertuzumab in combination with trastuzumab and docetaxel (experimental group). This study was dedicated to patients treated in the first-line therapy for metastatic disease. The primary endpoint of the study was progression-free survival (PFS); the secondary endpoints were overall survival (OS), overall response rate (ORR), and safety. The median time to progression was 18.5 months in the study arm and 12.4 months in the control arm ($p < 0.001$) and overall response rate, respectively, 80.2% and 69.3%. Significant benefit in prolonging survival has been demonstrated by adding pertuzumab to the treatment — the difference in the control group was up to 15.7 months, with median overall survival in the placebo arm 40.8 months and 56.5 months in the experimental arm ($p < 0.001$) [5].

The efficacy of pertuzumab was also demonstrated in two randomised trials in the neoadjuvant treatment of breast cancer: NeoSphere and TRYPHAENA. NeoSphere was a phase II study in which patients (n = 417) were randomly assigned to four groups and received preoperatively: trastuzumab in combination with docetaxel (group 1), pertuzumab in combination with trastuzumab and docetaxel (group 2), pertuzumab in combination with trastuzumab (group 3), or pertuzumab in combination with docetaxel (group 4) [6]. The primary endpoint was pathological complete response (pCR). In the group receiving both antibodies and docetaxel the pCR rate was 45.8% compared with 29% in the group receiving trastuzumab with docetaxel. After surgery, all patients in groups 1, 2, and 4 were given FEC chemotherapy in combination with trastuzumab, and group 3 was given sequential chemotherapy with docetaxel followed by FEC, also in combination with trastuzumab. The total duration of anti-HER2 treatment was one year. In the randomised phase II study, TRYPHAENA, patients (n = 225) were divided into three groups. In the first group patients received three cycles of neoadjuvant FEC chemotherapy (5-fluorouracil, epirubicin, cyclophosphamide) in combination with trastuzumab and pertuzumab, followed by three courses of docetaxel in combination with pertuzumab and trastuzumab; in the second group patients received three preoperative courses of FEC chemotherapy followed by three courses of pertuzumab in combination with trastuzumab and docetaxel. While in the third group patients received six pre-operative cycles of pertuzumab in combination with trastuzumab, docetaxel, and carboplatin (TCHP) [7]. After surgery, trastuzumab was used so that the total duration of anti-HER2 treatment was one year. Tolerability of treatment was the primary end point of TRYPHAENA study, while the secondary endpoint was the rate of pathological complete responses, which was 61.6% in the first group, 57.3 in the second group, and 66.2% in the third group. Based on the results of the above described studies, pertuzumab has been approved in the first-line treatment of HER2 positive metastatic breast cancer and in neoadjuvant therapy in HER2-positive breast cancer.

The use of pertuzumab is associated with a variety of more or less severe adverse events. Below are described the most common and most significant clinical complications associated with the use of pertuzumab: diarrhoea, neutropaenia and febrile neutropaenia, and cutaneous complications. We also provide procedure schemes in the event of their occurrence.

Pertuzumab adverse events

In the CLEOPATRA trial the most common adverse events reported in more than half of patients were diarrhoea, alopecia, and neutropaenia [4]. The most common adverse events in grade 3 to 4 according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE v. 3.) [8] were neutropaenia, neutropaenic fever, and leukopaenia. The most common serious adverse events included febrile neutropaenia, neutropaenia, and diarrhoea. The number of treatment-related deaths was similar in both groups — 1.2% of patients receiving pertuzumab and 1.5% of patients receiving placebo. These deaths were mainly caused by febrile neutropaenia and / or infection. Cutaneous toxicity was relatively frequent (Tab. 1, 2).

Cutaneous toxicity

The presence of HER2 receptor has been demonstrated in keratinocytes. As a result, the use of pertuzumab is associated with an increased incidence of skin lesions. In the CLEOPATRA study rash occurred in 45.2% of patients in the pertuzumab group and in 36% of patients in the placebo group. Most skin toxicities has been classified as either grade 1 or 2 adverse reactions according to NCI-CTCAE. These were most common during the first two cycles and resolved after treatment with systemic or topical medications [9]. In addition to rash, other skin complications observed in clinical trials involving pertuzumab were nail disease, pruritus, and dry skin. Patients receiving treatment with pertuzumab were infected with staphylococcus aureus, both sensitive and resistant to methicillin [10, 11]. In the registration study, the treatment of skin complications was necessary in 33.8% of patients treated in the control arm and in 45.9% of patients treated with pertuzumab. Steroids have been used in the case of rash, antibiotics (especially doxycycline) in nail infections, and antihistamines in patients who have itching. The proposed scheme for handling the case of acneiform rash is shown in Table 3.

Table 1. Pertuzumab toxicity in CLEOPATRA trial — all grades [4]

	Placebo + Trastuzumab + Docetaxel n = 397 (%)	Pertuzumab + Trastuzumab + Docetaxel n = 407 (%)
Diarrhoea	184 (46.3)	272 (66.8)
Alopecia	240 (60.5)	248 (60.9)
Neutropaenia	197 (49.6)	215 (52.8)
Nausea	165 (41.6)	172 (42.3)
Fatigue	146 (36.8)	153 (37.6)
Rash	96 (24.2)	137 (33.7)
Decreased appetite	105 (26.4)	119 (29.2)
Mucositis	79 (19.9)	113 (27.8)
Asthenia	120 (30.2)	106 (26.0)
Peripheral oedema	119 (30.0)	94 (23.1)
Constipation	99 (24.9)	61 (15.0)
Febrile neutropaenia	30 (7.6)	56 (13.8)
Dry skin	17 (4.3)	43 (10.6)

Table 2. Pertuzumab toxicity in CLEOPATRA trial- grade 3 or higher [4]

	Placebo + Trastuzumab + Docetaxel n = 397 (%)	Pertuzumab + Trastuzumab + Docetaxel n = 407 (%)
Neutropaenia	182 (45.8)	199 (48.9)
Febrile neutropaenia	30 (7.6)	56 (13.8)
Leukopaenia	58 (14.6)	50 (12.3)
Diarrhoea	20 (5.0)	32 (7.9)
Peripheral neuropathy	7 (1.8)	11 (2.7)
Anaemia	14 (3.5)	10 (2.5)
Asthenia	6 (1.5)	10 (2.5)
Fatigue	13 (33)	9 (2.2)
Granulocytopaenia	9 (2.3)	6 (1.5)
Left ventricular systolic heart failure	11 (2.8)	5 (1.2)
Dyspnoea	8 (2.0)	4 (1.0)

Table 3. Proposed treatment scheme for acneiform rash

Acneiform rash grade 1 according to CTCAE	Continuation of combination therapy	Observation, topical symptomatic treatment: clindamycin and possibly hydrocortisone in ointment
Acneiform rash grade 2 according to CTCAE	Continuation of combination therapy	Symptomatic treatment: Locally clindamycin + hydrocortisone in ointment until improvement (rash in 1 grade or no symptoms) + doxycycline orally 100 mg × 2 for at least 4 weeks or longer if symptomatic rash If the rash is accompanied by pruritus- antihistamines (e.g. loratadine 10 mg)
Acneiform rash grade 3 according to CTCAE	Suspension of combination therapy	Commencement of symptomatic treatment as in grade 2 Continuation of treatment with pertuzumab in case of improvement (symptom remission or reduction to grade 2) — re-induction of combination therapy

Table 4. The incidence of neutropaenia, and febrile neutropaenia in clinical trials with pertuzumab

%	CLEOPATRA (Palliative treatment)		NeoSphere (Neoadjuvant treatment)				TRYPHAENA (Neoadjuvant treatment)		
	TH (%)	THP (%)	TH (%)	THP (%)	HP (%)	TP (%)	FEC+H+P (%)	FEC (%)	TCP (%)
Neutropaenia (all grades)	49.6	52.8	63	50	1	63	51.4	46.7	48.7
Neutropaenia (grade 3 and/or 4)	45.8	48.9	5	45	1	55	47.2	42.7	46.1
Febrile neutropaenia	7.6	13.8	7	8	0	7	18.1	9.3	17.1

TH: docetaxel + trastuzumab; THP: docetaxel + trastuzumab + pertuzumab; HP: trastuzumab + pertuzumab; Docetaxel + pertuzumab; FEC + H + P: 5-fluorouracil + epirubicin + cyclophosphamide + trastuzumab + pertuzumab; Docetaxel + carboplatin + trastuzumab + pertuzumab

Important in the case of possible skin adverse events are prophylactic non-drug recommendations for rash and therapeutic treatment in the case of dry skin: showering with warm water and avoidance of prolonged hot bathing causing skin maceration, the use of oiling, hypoallergenic lotion, and emulsion for body, caution when cosmetic procedures such as manicure, pedicure — avoiding damage and infection of the surrounding area of the nail shaft.

Neutropaenia, febrile neutropaenia

In patients treated with pertuzumab, trastuzumab, and docetaxel, there is an increased risk of febrile neutropaenia compared to placebo, trastuzumab, and docetaxel. In the CLEOPATRA study, febrile neutropaenia occurred in 13.8% of patients treated with pertuzumab in the experimental arm, and in 7.6% in the control group [5]. This risk is elevated especially during the first three cycles of treatment — the highest after the first course, then it decreases. It is suspected that a higher incidence of febrile neutropaenia in patients treated with pertuzumab may be due to the increased incidence of mucosal inflammation and diarrhoea in these patients. Neutropaenia and febrile neutropaenia have been closely associated with chemotherapy — in the CLEOPATRA trial no febrile neutropaenia has been reported after discontinuation of docetaxel therapy.

Also in the NeoSphere and TRYPHAENA studies, neutropaenia and febrile neutropaenia were among the most common adverse events in grade 3 or higher (Tab. 4) [5–7]. It should be emphasised that in the event of neutropaenia and/or febrile neutropaenia, the principles of treatment do not differ from the ones recommended in the event of these complications following classic chemotherapy regimens. Also, in the combination of pertuzumab, trastuzumab, and docetaxel, the principles of neutropaenic prophylaxis using granulocyte growth factors (G-CSF) are mandatory. In clinical practice febrile neutropaenia prophylaxis recommendations developed by EORTC (2010 update) [12] and ESMO (2016) [13] or NCCN (2016) [14] recommendations for febrile neutropaenia treatment are used. The proposed treatment scheme for neutropaenia is presented in Table 5.

Diarrhoea

Pertuzumab blocks ligand-dependent heterodimerisation among other HER receptors, including EGFR, HER 3, and HER 4 [15], prevents ligand binding to EGFR, and leads to decreased EGFR on the surface of the neoplastic cells. Blocking of the EGFR receptor may result in excessive chloride secretion, which can consequently lead to absorption disorders and secretory diarrhoea similar to those seen with other EGFR inhibitors (TKis) [15, 16]. Analysis of the CLEOPATRA, TRYPHAENA, and NeoSphere studies has confirmed the risk of diarrhoea in all treatment regimens using pertuzumab [5–7]. In most patients, episodes of diarrhoea were observed in grade 1–2, usually during the first cycle of chemotherapy (median time to diarrhoea onset was eight days), the incidence of diarrhoea was reduced during subsequent cycles of treatment [17]. No grade 4 diarrhoea was observed [18]. Among patients who experienced diarrhoea, 40% received at least one anti-diarrhoea drug (usually loperamide). There were no significant delays in treatment, only 2% of patients treated in the CLEOPATRA study were excluded from treatment for diarrhoea and none of the patients treated for early breast cancer in the NeoSphere and Tryphen trials had their therapy discontinued because of diarrhoea. In patients less than 65 years old, the episode of diarrhoea did not result in delay or discontinuation of treatment. The mean incidence of diarrhoea incidents was greater during docetaxel treatment compared to treatment regimens without taxoids, especially in patients aged or more, who were more likely to develop diarrhoea in grade 3, with the risk of reducing the intensity of treatment. Rarely a relationship between diarrhoea and febrile neutropaenia could be observed. The highest probability of coexistence of such toxicities was noted for the TCH-P neoadjuvant regimen, the smallest for P + H, and patient age did not affect the incidence of this event. Gastrointestinal disorders (irritable bowel syndrome, intestinal mucosa, or Crohn's disease) were not associated with a higher risk of diarrhoea during treatment with pertuzumab. The proposed scheme to be followed in the event of diarrhoea is shown in Table 6.

Table 5. Proposed treatment scheme for neutropaenia

Neutropaenia Grade 1. CTCAE	Continuation of combination therapy	Blood test before each treatment cycle
Neutropaenia Grade 2. CTCAE	Suspension of combination therapy	Continuation of treatment when neutropaenia returns to grade 1 or lower Alternatively, reduction of the dose of docetaxel (not Trastuzumab!, not Pertuzumab!) For re-episodes of neutropaenia grade 2: Docetaxel dose reduction: — Initially from 100 mg/m^2 (if increased from the initial 75 mg/m^2 due to a good tolerance of the first course) to 75 mg/m^2 — In case of a recurrence the reduction from 75 mg/m^2 to 60 mg/m^2 Blood tests before each subsequent cycle Consider primary prophylaxis of neutropaenic fever (according to EORTC recommendations)
Neutropaenia Grade 3. CTCAE	Suspension of combination therapy	Continuation of treatment when neutropaenia returns to grade 1 or lower Alternatively, reduction of the dose of docetaxel (not Trastuzumab!, not Pertuzumab!) For re-episodes of neutropaenia grade 3; according to the above scheme Blood tests before each subsequent cycle Consider primary prophylaxis of neutropaenic fever (according to EORTC recommendations) Docetaxel dose reduction: • Initially from 100 mg/m^2 (if increased from the initial 75 mg/m^2 due to a good tolerance of the first course) to 75 mg/m^2 in case of a recurrence • In case of recurrence reduction from 75 mg/m^2 to 60 mg/m^2

Table 6. Proposed treatment scheme for diarrhoea

Diarrhoea Grade 1. CTCAE	Continuing treatment at unchanged dose	Symptomatic treatment (loperamide)
Diarrhoea Grade 2. CTCAE	Continuing treatment with docetaxel at a reduced dose	Symptomatic treatment (loperamide) + discontinuing administration of the drug until symptoms disappear or lessening the severity to Grade 1 Docetaxel dose reduction: • Initially from 100 mg/m^2 (if increased from the initial 75 mg/m^2 due to a good tolerance of the first course) at 75 mg/m^2 • In case of a recurrence, the reduction from 75 mg/m^2 to 60 mg/m^2
Diarrhoea Grade 3. CTCAE	Suspension of combination therapy	Intravenous electrolyte supplementation + symptomatic treatment + discontinuation of treatment until asymptomatic (grade 0) or diarrhoea reduction to grade 1 Re-induction with co-administration of docetaxel at reduced dosage Docetaxel dose reduction: • Initially from 100 mg/m^2 (if increased from the initial 75 mg/m^2 due to a good tolerance of the first course) at 75 mg/m^2 • In case of a recurrence, the reduction from 75 mg/m^2 to 60 mg/m^2
Diarrhoea Grade 4. CTCAE	Persistent discontinuation of treatment. Continuing treatment with docetaxel at a reduced dose justified for consideration only in the case of significant clinical benefit with excellent co-operation with the patient	Intravenous electrolyte supplementation + symptomatic treatment + discontinuation of treatment till asymptomatic (grade 0) or diarrhoea reduction to grade 1

Prior to the implementation of therapy, where there is an increased risk of diarrhoea, and during its pharmacological treatment, patients should be advised of proper nonpharmacological treatment: eating small portions, drinking 2–3 litres of fluid throughout the day, eliminating dietary supplements and foods with high osmolarity and spicy food. Such treatment may help to overcome this toxicity.

Summary

Introduction of pertuzumab to the treatment of patients with breast cancer with HER2 overexpression and/or HER2 gene amplification, significantly improved outcomes in this poor-prognosis population [5–7]. The use of this humanised monoclonal antibody targeting the extracellular dimerisation domain (subdomain II) of human epidermal growth factor receptor type 2 produces a synergistic effect with trastuzumab. However, the use of pertuzumab is associated with the occurrence of adverse events of varying severity. Some of them are toxicities previously unknown in this class of drugs. These include especially skin toxicity, neutropaenia, febrile neutropaenia and diarrhoea. Treatment regimens for the occurrence of these adverse events are proposed in this article. These toxicities are characteristic for the use of pertuzumab in combination with trastuzumab and docetaxel. Therefore, in each case, attempts are required to identify the direct compound responsible for the onset of the adverse events with careful evaluation and treatment. Since these toxicities are usually present in combination therapy of anti-HER2 antibodies with chemotherapy, careful consideration should be given to the possible termination of pertuzumab therapy. The reduction of docetaxel dose or termination of cytostatic therapy and an attempt to continue targeted therapy should always be considered.

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