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Neoadjuvant treatment in a patient with HER2-positive breast cancer — a case study and review of recent recommendations

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ABSTRACT

Pre-operative breast cancer therapy (neoadjuvant or induction) is reserved for patients with locally advanced tumours primarily amenable to surgery (neoadjuvant treatment) or subjects with initially unresectable disease in whom respectability may be achieved following upfront systemic treatment (induction therapy). Initial systemic treatment may be used in all phenotypes of breast cancer. Patients with “triple-negative” breast cancer (TNBC) or human epidermal growth factor receptor 2 (HER-2)-positive tumours benefit most from preoperative therapy. Patients in this group most often achieve pathological complete response (pCR), which results in an improved prognosis. In this report, we present a case of complete tumour regression following neoadjuvant chemotherapy combined with trastuzumab (currently a non-reimbursed indication in Poland) and we review the literature on this issue.

Key words: breast cancer, neoadjuvant treatment, trastuzumab, pathological complete response

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Introduction

The standard approach to breast cancer therapy mostly involves combination treatment including surgery and — depending on additional prognostic and predictive factors — chemotherapy, immune therapy, radiotherapy, and hormonal therapy. Neoadjuvant and adjuvant chemotherapy have been considered equally effective, both having similar activity in terms of survival improvement in patients primarily amenable to surgery [1]. In non-resectable patients, induction therapy facilitates surgery, whereas neoadjuvant chemotherapy in resectable disease allows reduction of the extent of surgery and preserving the breast. Tumours that are human epidermal growth factor receptor 2 (HER2)-positive are found in about 20% of patients with breast cancer. The HER2 status is determined by expression of receptor tested with the use of immunohistochemistry and categorised as negative (0 or 1+) or positive (3+). Borderline category (2+) requires *HER2* gene copies

assessment with the use of fluorescence in situ hybridisation (FISH). HER2-positive breast cancer is associated with a more aggressive disease, shortened disease-free survival following radical therapy, and reduced overall survival. At the same time, overexpression or amplification of the *HER2* gene is a predictive factor for response to treatment with the monoclonal antibody trastuzumab. Trastuzumab binds to an extracellular domain of the HER2 receptor on the surface of a cancer cell and it inhibits an intracellular signalling pathway associated with the function of the HER2 receptor by arresting the cell cycle in the G1/S phase [2]. Upon HER2 receptor binding with trastuzumab, HER2-trastuzumab complexes are internalised and degraded, resulting in a reduction of the number of HER2 receptors on the cell surface. In addition, due to its structure (an IgG1 antibody), trastuzumab exerts an immune-mediated clinical activity, mostly antibody-dependent cellular cytotoxicity (ADCC) [3]. A meta-analysis of phase III clinical trials showed that the addition of trastuzumab to postopera-

tive chemotherapy resulted in a 40% relative recurrence risk reduction and a 36% relative mortality risk reduction compared to chemotherapy only [4]. The optimal duration of postoperative trastuzumab therapy is 12 months [5, 6]. Combining trastuzumab and neoadjuvant chemotherapy may result in pathological complete response (pCR) in a significant proportion of patients with locally advanced HER2-positive breast cancer, which is associated with prolonged disease-free survival [7]. Based on these findings, our patient received trastuzumab as part of pre-surgical breast cancer therapy.

Case report

A 65-year-old woman noticed a small lump in her right breast and an enlarged axillary lymph node on the right side in May 2014. The lump began to grow rapidly. After a month, the patient presented to her family physician and was referred to an oncology clinic. Physical examination revealed a poorly mobile tumour with a diameter of approximately 3 cm within the upper external quadrant of the right breast. Neither skin involvement nor nipple inversion was found. A packet of poorly mobile lymph nodes was noted in the right axilla. Mammography (May 12, 2014) showed a suspicious 25 × 20-mm mass in the upper external quadrant of the right breast. A core-needle biopsy of the mass in the right breast was performed (June 6, 2014) and it resulted in a diagnosis of “Poorly differentiated, invasive solid G3 carcinoma, with foci of comedo necrosis and severe lymphoid cell infiltration. Non-special type (NST), oestrogen receptor (ER), and progesterone receptor (PR) negative. HER2 positive (score 3+, complete membrane staining and cytoplasmic staining), Ki-67 75%”. Breast ultrasound revealed an irregular mass with a diameter of approximately 15 mm, and a 38 × 25-mm packet of lymph nodes in the axillary segment of the right breast. Other imaging studies (chest radiography, abdominal ultrasound) showed no evidence of cancer spread. The initial staging was cT2N2M0. The patient was in a good general condition (ECOG score 1). The decision was made to proceed with neoadjuvant chemotherapy. Due to the availability of trastuzumab (free drug sample), a 4 × AC-4 × TH regimen (4 × doxorubicin + cyclophosphamide, followed by 4 × docetaxel + trastuzumab) in standard doses was used in accordance with clinical trial results. The treatment was completed as scheduled. Neoadjuvant chemotherapy was administered from Jul 10, 2014 to Dec 12, 2014. The patient underwent regular cardiac monitoring, with serial ECG and echocardiography before and during treatment. Left ventricular ejection fraction remained stable at about 60%. Following the first four AC cycles, breast ultrasound was performed and showed a partial response.

Breast ultrasound was repeated again upon completion of pre-surgical therapy, showing no mass reported in the initial study in July 2014. A single, oval, hypoechogenic lymph node without the hilum was described at the border of the axillary segment of the right breast and the lower axilla. The patient was referred for surgery and right-sided mastectomy with axillary lymphadenectomy was performed on Jan 2, 2015. The postoperative pathology report indicated pCR, staged at ypT0N0. Further adjuvant therapy included radiotherapy and trastuzumab treatment was continued.

Discussion

Multiple studies on pre-surgical treatment with trastuzumab have been published. The most relevant examples of various options of neoadjuvant anti-HER2 therapy include the NOAH, NeoSphere, and NeoALTTO studies. The results of multicentre randomised NeOAdjuvant Herceptin (NOAH) study were published in 2010 [7]. The aim of this study was to evaluate the clinical efficacy of trastuzumab combined with neoadjuvant chemotherapy containing anthracyclines and taxanes, followed by continuation of trastuzumab treatment until reaching an overall treatment duration of one year. The study included patients with locally advanced breast cancer, including inflammatory breast cancer. Patients with HER2-positive breast cancer were randomised to neoadjuvant chemotherapy (doxorubicin, paclitaxel, cyclophosphamide, methotrexate, fluorouracil) or to chemotherapy combined with trastuzumab, followed by one-year postoperative trastuzumab treatment. Significantly increased rates of three-year overall survival (87% vs. 74%, $P = 0.009$), pCR (38% vs. 19%, $P = 0.001$), and three-year survival free from an event (death or disease progression) (71% vs. 56%, $P = 0.013$) were noted in the combined chemotherapy-trastuzumab arm compared to chemotherapy only. Reduction of the tumour size allowed radical breast-sparing surgery in most patients. In addition, postoperative pathological evaluation showed pCR in about 30% of patients. Overall and progression-free survival were significantly increased in patients with pCR compared to those without pCR within the breast and axillary lymph nodes (70% vs. 53% during a 3-year follow-up, $P = 0.0006$). Trastuzumab treatment was well tolerated. Despite combined use of trastuzumab and doxorubicin, symptomatic heart failure was observed in only 2% of patients. Four years after the initial publication, Gianni et al. summarised the long-term benefits of neoadjuvant trastuzumab treatment in patients with HER2-positive breast cancer, showing an improved survival in those receiving trastuzumab preoperatively and confirming the importance of pCR as a prognostic factor in this patient group [7].

Dual HER2 blockade with trastuzumab and lapatinib or pertuzumab combined with induction chemotherapy was evaluated in the Neoadjuvant Lapatinib and/or Trastuzumab Treatment Optimisation (NeoALTTO) and Neoadjuvant Study of Pertuzumab and Herceptin in an Early Regimen Evaluation (NeoSphere) studies [8, 9]. In the Neo-ALTTO study, patients selected for preoperative therapy received paclitaxel combined with trastuzumab, lapatinib, or both. Combined treatment was preceded with a six-week molecular targeted therapy. The highest pCR rate was achieved in patients treated with trastuzumab and lapatinib (51.3%), which was significantly higher compared to any anti-HER2 monotherapy groups. In contrast, no significant difference in the pCR rate was noted between patients treated with trastuzumab or lapatinib [8]. In the four-arm NeoSphere study, patients received docetaxel with trastuzumab, docetaxel with trastuzumab and pertuzumab, trastuzumab with pertuzumab, or docetaxel with pertuzumab. The highest pCR rate (45.8%) was observed in the three-drug arm, which was significantly higher compared to all other evaluated therapeutic options. Interestingly, pCR was achieved in about 17% of patients treated with anti-HER2 drugs only. Subgroup analysis showed that regardless of the treatment used, pCR rates were significantly higher in patients with ER-negative tumours.

When discussing pCR, its precise definition is of importance. Some authors define pCR as the response achieved in the breast tumour itself, while others also consider regression within axillary lymph nodes [10]. The presence of non-invasive lesions in postoperative samples is also subject to varying interpretation, which may partially explain discrepant results of the meta-analyses of phase II and III clinical trials regarding pCR. Von Minckwitz concluded [11] that only pCR defined as ypT0ypN0 is associated with improved long-term survival, while ypTis, ypT1mic, and ypN+ responses are associated with high recurrence risk and should not be considered pCR. Currently, as many as half of patients may achieve pCR following pre-surgical treatment. Achievement of pCR is associated with improved prognosis, as confirmed during several years of follow-up [12]. However, the results of published studies are not entirely clear. In most cases, pCR was shown to be a predictor of long-term survival. Studies are not available that directly compare trastuzumab combined with adjuvant chemotherapy versus neoadjuvant and adjuvant chemotherapy. Additionally, these treatment regimens were not compared with trastuzumab therapy used only preoperatively, taking into account the proven postoperative efficacy of this drug [4].

In 2012, a meta-analysis of seven randomised clinical trials evaluating the response to neoadjuvant therapy and the effect of this response on long-term survival was published in the *Journal of Clinical Oncology*. Overall,

more than 6300 patients treated for breast cancer were included in that analysis [11]. The patients were divided into subgroups based on biological breast cancer subtypes (luminal A, luminal B, HER2-positive non-luminal, and basal). It was shown that achievement of pCR in slowly proliferating tumours has no prognostic value, while in subgroups with high Ki-67% values, pCR following neoadjuvant therapy identifies patients with a better prognosis. The highest prognostic value of pCR was shown for the HER2-positive (non-luminal) subtype and TNBC. In these subtypes, achievement of pCR improved prognosis to a degree comparable with the luminal A subtype. Similar results were reported by Cortazar in 2014 [13].

A retrospective Japanese study published in 2014 suggested a better prognosis in patients with HER2-positive and ER-positive tumours despite a lower rate of pCR compared with patients with ER-negative tumours [14]. In 204 patients who received preoperative trastuzumab treatment, pCR had no significant prognostic values in the ER-positive group (hazard ratio 0.63; $P = 0.56$). When considered regardless of the ER status, patients with HER2-positive tumours who received trastuzumab combined with chemotherapy achieve pCR twice as often compared to chemotherapy only.

Following preoperative immunochemotherapy, trastuzumab treatment was continued in most studies until the total treatment duration of one year, and this is the currently recommended approach to the treatment of HER2-positive breast cancer [15]. Studies are lacking to answer the question of whether adjuvant trastuzumab therapy might be abandoned in patients receiving trastuzumab preoperatively.

Adjuvant therapy in patients with locally advanced breast cancer included radiotherapy, and hormonal therapy in patients with hormone receptor-positive tumours. Based on the current knowledge, even more individualised treatment approaches may be anticipated in the future, e.g. neoadjuvant therapy in patients with early HER2-positive breast cancer [16], interruption of anti-HER2 therapy in patients with pCR, or modification of anti-HER2 therapy in patients without pCR. Regardless of the search for novel approaches to the treatment with anti-HER2 drugs, simultaneous inhibition of other pathways, e.g. associated with ER, vascular endothelial growth factor (VEGF), mTOR, or PI3K kinase, may lead to a further increase in the rate of pCR in patients with HER2-positive breast cancer [17]. Prospective randomised studies will answer whether this patient group may avoid surgery or adjuvant radiotherapy [18].

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