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ORIGINAL ARTICLE

Do we really know how to overcome trastuzumab resistance in hormone sensitive metastatic breast cancer?

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Summary

Purpose: *This article focuses on how the status of hormone receptors (HR) influences the efficacy of trastuzumab in patients with metastatic HER2-positive breast cancer treated with first-line trastuzumab in combination with taxane-based chemotherapy.*

Methods: *A prospective study was carried out at the Clinic for Oncology, Clinical Centre in Nis, from January 2015 to until June 2018. A total of 121 patients were treated with first-line trastuzumab in combination with taxane-based chemotherapy. None of the patients from the HR-positive group received hormonotherapy after completion of chemotherapy with trastuzumab.*

Results: *Clinical benefit rate was present in 76% of the patients, including partial response (PR) in 37%, stable disease (SD) in 38%, and complete response (CR) in almost 8% of the patients. Progressive disease (PD) occurred in almost a quarter of the patients, i.e. 24%. Progression-free survival (PFS) in the entire group of patients amounted to 9 months, whereas overall survival (OS) was 30 months. PFS in the HR-negative tumor group was significantly longer (13 months) compared to 8 months in the HR-positive tumor group (p<0.0001; HR 0.49;95% CI 0.31-0.69). Furthermore, OS was significantly longer in the HR-negative tumor group (34 months), compared to 26 months in the HR-positive tumor group (p=0.0073, HR 0.57; 95% CI 0.36-0.90).*

Conclusions: *These data indicate a different response to anti-HER2 therapy in patients with HER2+ metastatic breast cancer (MBC) according to HR status, thus emphasizing that ER most likely represents an escape pathway for the response to anti-HER2 target therapy and vice versa. Combining hormonotherapy with anti-HER2 therapy surely represents a promising strategy which could help overcome resistance to trastuzumab and other anti-HER2 agents.*

Key words: *clinical benefit rate, hormone receptor, overall survival, progression-free survival, trastuzumab*

Introduction

Breast cancer falls into a quite heterogeneous group of diseases. Four molecular subtypes of breast cancer have been identified based on the expression of genes: basal-like, luminal A, luminal B and human epidermal growth factor 2 (HER2)-positive breast cancer. These four molecular subtypes are very similar to the clinical classification which is based on the status of estrogen receptor (ER) and progesterone receptor (PR), the overexpression of HER2 receptors as well as tumor grade and proliferative activity [1]. HER2-positive breast cancer comprises 15-30% of all invasive breast cancers and has a high risk of recurrence and a relatively poor prognosis.

About half of HER2-positive breast cancers are hormone receptor (HR)-positive and the majority

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of them belongs to luminal B carcinomas based on gene expression [2,3]. Nowadays, trastuzumab is the standard treatment in HER2-positive MBC, and almost all studies to date were designed to test the combination of trastuzumab with chemotherapeutic protocols no matter the status of HRs, meaning that the therapy was not optimized for HR-positive carcinomas. Only a few studies tested the combination of trastuzumab with hormonotherapy in patients with HR+/HER2-positive breast cancer [4,5].

This article focuses on HER2-positive MBC divided into HR-positive and HR-negative, as well as on the effect the expression of HRs have on the outcome of first-line trastuzumab treatment for metastatic HER2-positive breast cancer. At present, there are extensive data from preclinical and clinical trials indicating a complex bidirectional crosstalk between ER and HER2 signaling pathways [6,7]. This bidirectional crosstalk is probably the main mechanism of resistance to trastuzumab in this breast cancer subtype. However, the effect of HR co-expression on the outcome of different anti-HER2 therapies in MBC is still unknown [8,9].

Methods

A prospective study was carried out at the Clinic for Oncology, Clinical Centre in Nis, from January 2015 until June 2018 in order to examine the influence of the status of HRs on the efficacy of trastuzumab in patients with metastatic HER2-positive breast cancer treated with first-line trastuzumab in combination with taxane-based chemotherapy. All patients started therapy in January 2015 and were monitored until June 2018. They had to be over 18 years of age and present HER2 overexpression (IHC 3+) or, if the expression was moderate (IHC2+), they needed to have a confirmed gene amplification (CISH positive) since this group of patients benefited most from trastuzumab. Given that the indications of the Health Insurance Fund in Serbia are such that patients can receive trastuzumab with taxanes only if previously treated with anthracyclines, all patients treated with anthracyclines for early or locally advanced breast cancer received the aforementioned therapy as first-line treatment for MBC. Patients who were initially diagnosed as stage IV first had to receive 4 cycles of AC protocol (Doxorubicin 60 mg/m^2, Cyclophosphamide 600 mg/m^2) or FAC protocol (5 Fluorouracil 500 mg/m^2, Doxorubicin 50 mg/m^2, Cyclophosphamide 500 mg/m^2). The initial left ventricular ejection fraction (LVEF) had to be higher than 50%. Eligible patients needed to have Eastern Cooperative Oncology Group (ECOG) performance status 0-1, expected survival more than 3 months and measurable disease according to RECIST 1.1 criteria. Blood tests, as well as renal and liver functions had to meet the following criteria for the administration of therapy: hemoglobin >10 g/dL ; neutrophil count >2.0×10^9 cell/L; platelet count >100x×10^9 cell/L; creatinine < 1.5×upper limit of normal (ULN); aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) < 2.5×ULN; and alkaline phosphatase <5×ULN .

Therapy

Intravenous administration of 80-100 mg/m^2 of docetaxel or 175 mg/m^2 of paclitaxel were given for a maximum of 6-8 cycles in combination with subcutaneous doses of 600 mg of trastuzumab, after which the therapy was continued only with trastuzumab until progression of disease. All patients received premedication before the administration of taxanes in the form of corticosteroids (dexamethasone or prednisolone) and antihistamines (chloropyramine). The effects of therapy were evaluated every 3-4 cycles using computed tomography or magnetic resonance imaging following RECIST 1.1 criteria based on which the response was defined as progressive disease (PD), stable disease (SD), partial remission PR or complete remission (CR).

Statistics

The obtained results were entered into a prospective database, arranged in tables and presented in the form of charts. As far as descriptive statistics was concerned, the data were presented in the form of absolute and relative numbers.

The primary aim of this study was to examine the disease outcome, the PFS, the OS and the clinical benefit rate (CBR) in the entire group of patients, as well as to examine differences in disease outcome in patients with different HR status (HR+/HER+, ER+ and/or PR+/HER2+) compared to HER-/HER2+ (ER-/PR-/HER2+).

PFS was defined as the time from the first dose of systemic trastuzumab to disease progression or death without disease progression. OS was defined as the time from the first dose of trastuzumab to fatal outcome. Therapeutic response (CBR) was the percentage of patients with complete remission (CR) + partial remission (PR) + stable disease (SD). A record had to be kept of the exact date of the first trastuzumab therapy as well as the exact date of the disease progression or fatal outcome, if it occurred. Based on these data, the Kaplan-Meier method for PFS and OS was performed in the tested groups. The groups were formed on the basis of HR status. Log rank test was used to compare PFS and OS of the formed groups. Statistical significance was set at $p<0.05$.

Results

This study included 121 HER2-positive patients with MBC who were treated at the Clinic for Oncology of the Clinical Centre Nis from January 2015 to June 2018 and prospectively entered into a database. All patients were treated with first-line trastuzumab in combination with taxane-based chemotherapy. They were divided into two groups: HR-positive, which included 65 patients (53.7%), and HR-negative, which consisted of 56 patients (46.4%). None of the patients from the HR-positive group received hormonotherapy after

Table 1. Patient characteristics (n=121)

Charasteristics	*n (%)*
Median age, years (range)	56 (27-80)
HR status	
HR positive	65 (53.7)
HR negative	56 (46.4)
HER2 status	
IHC 3+	111 (91.7)
IHC 2+	10 (8.3)
Initial disease stage	
I-III	68 (56.2)
IV	53 (43.8)
Number of metastatic sites	
1	71 (58.7)
2	43 (35.5)
≥3	7 (5.8)
Type of taxanes with trastuzumab	
Paclitaxel	81 (66.9)
Docetaxel	40 (33.1)

IHC: immunohistochemistry; All patients with IHC 2+ positivity had chromogenic in situ hybridization-proven HER2 amplification

completing chemotherapy with trastuzumab. The basic characteristics of the patients are shown in Table 1. In 111 patients (91.7%), HER2 status was confirmed as IHC3+, while only 10 patients (8.3%) were IHC2+ CISH positive. Recurrence of initially treated early breast cancer appeared in 56% of the patients, whereas the disease was initially diagnosed in stage IV in 44% of the patients.

Table 2 shows that CBR was present in 76% of the patients, including PR in 37%, SD in 38%, and CR in almost 8% of the patients. PD occurred in almost a quarter of the patients, i.e. 24%.

Table 2. Response to therapy

Responses	*n (%)*
Complete response (CR)	9 (7.4)
Partial response (PR)	45 (37.2)
Stable disease (SD)	38 (31.4)
Progressive disease (PD)	29 (24)
Clinical benefit rate (CBR)	92 (76)
Objective response rate (ORR)	54 (44.6)

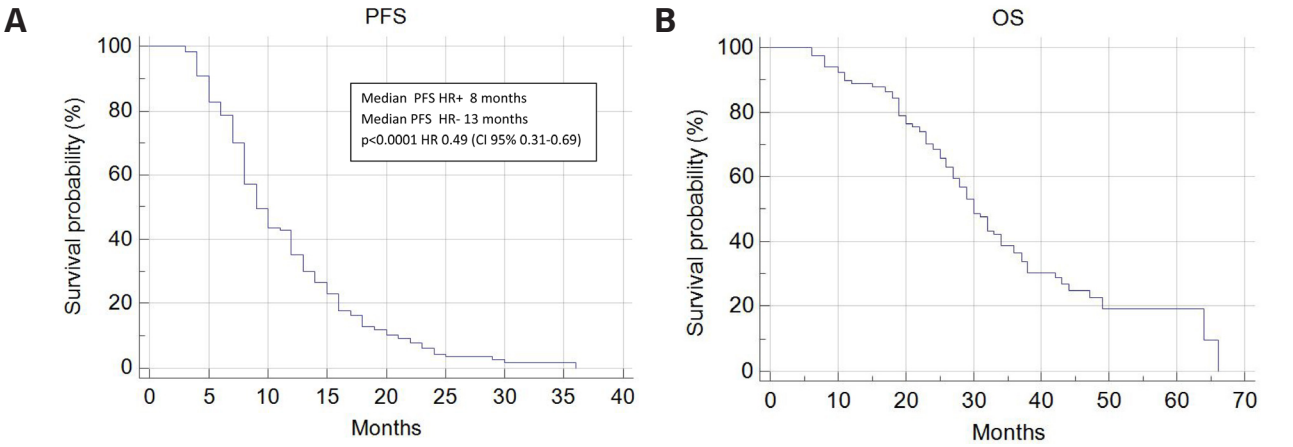

Figure 1. A: Progression-free survival. **B:** Overall survival.

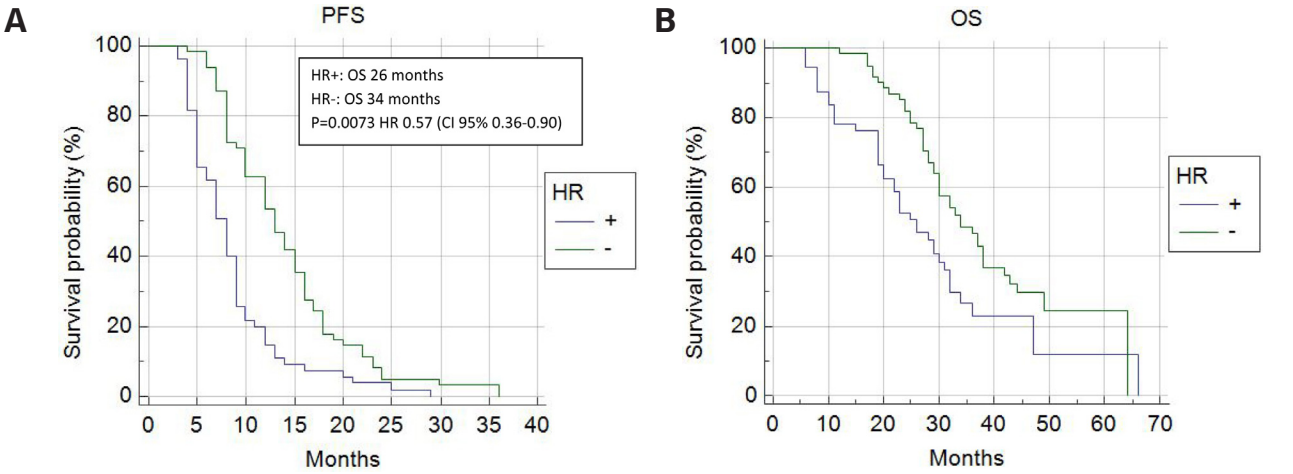

Figure 2. A: Progression-free survival according to hormone receptor status. **B:** Overall survival according to hormone receptor status.

PFS of the entire group of patients amounted to 9 months (Figure 1A), whereas OS was 30 months (Figure 1B).

PFS in the HR-negative tumor group was significantly longer, i.e. 13 months, compared to 8 months in the HR-positive tumor group (p<0.0001), as shown in Figure 2A. Furthermore, OS was significantly longer in the HR-negative tumor group (34 months, in comparison to the HR-positive tumor group, 26 months; p=0.0073), as presented in Figure 2B.

PFS and OS were significantly longer in patients who had better response to therapy (p<0.0001).

Discussion

This prospective study analyzed the outcome of first-line trastuzumab treatment for metastatic HER2-positive breast cancer in 121 patients according to the status of HR. Our results suggest that the benefit of trastuzumab treatment in combination with chemotherapy depends on the status of steroid receptors and that patients with HR-negative tumors have significantly longer PFS and OS.

Objective response rate (ORR) was 44% in the entire group of patients, with CR rate of 7% and PR rate of 37%, which is somewhat lower than in a pivotal study by Marty et al. in which ORR was 61% in the docetaxel and trastuzumab group, with CR being 7% and PR 54%. The number of HR-positive patients was similar – 56% – compared to 54% in our study [11]. With regard to objective response, our results are also comparable to the results of a pivotal study by Slamon et al. who compared the efficacy of trastuzumab combined with paclitaxel versus paclitaxel alone as first-line treatment for HER2-positive MBC. In the H0648g study ORR increased to 49% in the trastuzumab group compared to only 17% in the docetaxel group [12,13]. The results of these two clinical studies actually introduced the combination of trastuzumab and taxane-based chemotherapy into clinical practice. They showed that PFS and OS were considerably longer in combination with trastuzumab. PFS was 11.7 months in combination with docetaxel, and 7 months in combination with paclitaxel. Our results are comparable with the results of these two registration studies given that PFS was 9 months and that two thirds of the patients received paclitaxel ,whereas one third received docetaxel. OS ranged between between 2 and 2.5 years, i.e. 31 and 25 months, whereas in our study it amounted to 30 months [11-13].

What is crucial about our study is that we managed to find a significant link between HR status and the outcome of first-line trastuzumab treatment for HER2-positive MBC. Before discussing these results, we would like to mention certain limitations of this study. Data were collected only from patients who did not receive hormonotherapy as maintenance therapy for HR-positive tumors after chemotherapy with trastuzumab. We are aware that no clinical study was ever designed to have hormonotherapy as maintenance therapy, therefore recommendations are not strong, and clinicians are left to decide whether to administer it or not. The aim was to see if HR-positive patients have worse trastuzumab treatment outcome and to emphasize as recommendation to our institution that the blockage of both signaling pathways of HER2 and ER would contribute to a significantly better treatment outcome in this group of patients.

Although some groups of authors compared the outcome of trastuzumab treatment according to HR status, their results are relatively inconsistent. Brufsky et al. retrospectively analyzed all patients who received trastuzumab in combination with chemotherapy for MBC within clinical studies including pivotal trials. The authors reached a conclusion that patients with HR receptor-positive tumors and patients with HR-negative tumors benefited equally from trastuzumab in combination with chemotherapy. Response rate and PFS were not different according to the status of HR [12,14]. On the other hand, in a different study, Montemurro et al. included 227 patients treated with trastuzumab in combination with chemotherapy for MBC and concluded that a high expression of ER (30% of tumor cells) is a strong predictor of a lower probability of response to trastuzumab with hormonotherapy (HR 0.422, p<0.009). In patients with HR-positive tumors (1% of tumor cells), maintenance therapy which included hormonotherapy with trastuzumab after completing chemotherapy was linked with considerably longer PFS (p<0.007). The authors concluded that, as assumed, there two subtypes within HER2-positive tumors based on HR status, which not only differ in prognosis, but are also a strong predictor of response to anti-HER2 therapy [10]. Moreover, that interaction between HER2 and ER signaling pathways is a one way to avoid HER2 inhibition. The interaction is bidirectional since it is known that HER2-positive carcinomas can be highly resistant to chemotherapy, which further indicates that the optimal control of HER2-positive and HR-positive carcinomas requires simultaneous inhibition of both signaling pathways [15-17]. The first studies that examined the combination of aromatase inhibitors and anti-HER2 trastuzumab or lapatinib therapy showed that patients who received hormonotherapy with anti-HER2 therapy had a significantly better response rate and PFS

compared to those who received hormonotherapy alone. Patients who were treated with anastrozole and trastuzumab had better PFS (4.8 vs 2.4 months; p=0.0016), ORR (20.3 vs 6.8%; p=0.018), and CBR (42.7 vs 27.9%, p=0.026) compared to anastrozole alone. In fact, these studies were the ones that established the proof of principle and basis for future research in the treatment of HER2- positive/HR-positive tumors [5,18,19].

On the other hand, in a retrospective study including 588 HER2-positive patients with MBC, a group of Chinese authors showed that a group of HR+/HER2+ patients treated with trastuzumab in combination with chemotherapy had the best treatment outcome. OS in this group amounted to 48.3 months, compared to 40.9 months in a HR-/HER2+ group of patients treated with the same therapy, 26.2 months in a HR+/HER2+ group of patients who did not receive trastuzumab, and 20.0 months in a HR+/HER2+ group of patients who did not receive trastuzumab as well (p<0.0001) [20]. Another retrospective observational study that included 164 women who received first-line trastuzumab treatment showed that HR+ tumors had greater treatment benefits [21]. Bonotto et al. showed in their retrospective analysis of patients treated with up to fourth-line therapy MBC that the HR+/HER2+ group had a better treatment outcome (PFS 17.5 months vs 8.1 months, OS 55.3 months vs 26 months, for HR+ HER2+ and HR-HER2+ subset, respectively) [22].

One large prospective observational study on more than 1000 patients revealed the significance of the dual blockade of HER2 and ER signaling pathways, with or without chemotherapy, since PFS and OS were considerably longer in the group with hormonotherapy and anti-HER2 therapy, compared to the group with anti[-]HER2 therapy alone [23]. The EGF104900 study that included pre-treated HER2+ patients showed that only ER patients benefited from the dual blockade. These results support the hypothesis that the ER signaling pathway is one of the mechanisms of resistance to HER2 target therapy or, in other words, the absence of ER expression can increase HER signaling dependence [24,25].

The aforementioned data indicate a different response to anti-HER2 therapy in patients with HER2+ MBC according to HR status, thus emphasizing that ER most likely represents an escape pathway for the response to anti-HER2 target therapy and *vice versa*. Combining hormonotherapy with anti-HER2 therapy surely represents a promising strategy which could help overcome resistance to trastuzumab and other agents. Studies on metastatic tumors suggest that HER+/HER2+ carcinomas are a different entity from HR-/HER2+ carcinomas and that future randomized studies should focus on the combination of hormonotherapy and different anti-HER2 therapies to find an optimal therapeutic approach to this subgroup of patients.

Conflict of interests

The authors declare no conflict of interests.

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