Original article

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ESTROGEN RECEPTOR AS A RESISTANCE MECHANISM TO TRASTUZUMAB

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HER2-positive hormone-sensitive (HER2+/HR+) breast cancers have recently been singled out as a separate entity. It has been suggested that elevated estrogen receptor (ER) expression and/or activity may represent an avoidance mechanism or an alternative pathway leading to resistance to anti-HER2 therapy.

The aim of the study was to examine the disease outcome as the clinical benefit rate (CBR), progression-free survival (PFS), and overall survival (OS), both in the group of patients with HER2-positive metastatic breast cancer treated with first-line systemic therapy of trastuzumab along with chemotherapy and in patients with different status of hormone receptors HR+/HER2+ (ER+ and/or PR+/HER2+) compared to HR-/HER2+ (ER-/PR-/HER2+).

The study included 121 patients with pathohistologically confirmed HER2+ metastatic breast cancer treated with trastuzumab along with chemotherapy during 2017 and monitored until June 2020.

The mean age of the patients was 55.45 ± 9.83 years. 53.7% of the patients were HR-positive and 46.3% HR-negative. Progression-free survival was statistically significantly different regarding the HR status. Patients with HR- have longer PFS compared to patients with HR + (15 and 8 months, respectively). Patients with HR- tumors have a 62% lower risk of disease progression compared to HR+ tumors (HR 0.382; 95% CI 0.261-0.558, $p < 0.001$). The overall survival was statistically significantly different regarding the HR status ($p = 0.034$). Patients with HR- have longer survival compared to patients with HR+ (43 and 35 months, respectively). Hormone receptor negative tumors have a 43% lower risk of fatal outcome compared to hormone-sensitive tumors (HR 0.576; 95% CI 0.342-0.972, $p = 0.039$).

Given that HR+/HER2- tumors have a poorer outcome with trastuzumab treatment, future clinical trials should focus on the combination of hormonotherapy and anti-HER2 therapy in this subtype of breast cancers.

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Introduction

Nowadays, breast cancer (BC) is a global problem given the fact that the incidence has suggested an epidemic and that the consequences affect all parts of society, starting from health, social, economic, as well as other factors. Breast cancer accounts for 25% of the total malignancy of the female population, i.e. it participates with 15% in mortality due to its malignancy in women (1).

HER2-positive breast cancer is characterized by a biologically aggressive clinical course, shorter progression-free survival, and shorter overall survival compared to HER2-negative breast cancer (2, 3). The discovery of efficient anti-HER2 therapies, new monoclonal antibodies that block the HER2 signalling pathway more effectively, which significantly prolonged the survival of HER2-positive breast cancers with a median of 56 months, is a historic result in the treatment of metastatic breast cancer (4). Trastuzumab is the first monoclonal antibody to be approved for the treatment of metastatic breast cancer, and in the last decade several more monoclonal antibodies, as well as small molecules of tyrosine inhibitors, have been approved (5).

HER2-positive hormone-sensitive (HER2+/HR+) cancers have recently been singled out as a

separate entity. It has been suggested that elevated estrogen receptor (ER) expression and/or activity may represent an avoidance mechanism or an alternative pathway leading to resistance to anti-HER2 therapy (6, 7). Therefore, to see a potential role of ER as one of the mechanisms of resistance to trastuzumab, different HER2-positive breast cancer cell lines with *de novo* or acquired resistance after trastuzumab administration were examined. It has been observed that with constant inhibition of HER2 receptors, ER represents an alternative pathway by which HER2-positive cell lines proliferate and survive. The results of these cell line studies indicated that a more efficient blockade of these signalling pathways through the inhibition of both signalling pathways, HER2 and ER (8, 9), is necessary.

Studies conducted in early and locally advanced HER2-positive breast cancer have shown a correlation between the hormone receptor (HR) status and the efficacy of anti-HER2 therapy (10, 11). If the expression of hormone receptors, especially ER, is one of the mechanisms of resistance to trastuzumab and if this study shows that HR+/HER2+ patients treated with standard trastuzumab and chemotherapy have a worse disease outcome, i.e. shorter progression-free survival and overall survival compared to HR-/HER2+, it will indicate that further strategy of treatment of this subgroup of patients and further clinical research should focus on the combination of anti-HER2 and hormonotherapy that could represent a new standard in treatment. Hence, with the use of anti-HER2 and hormonotherapy, the use of cytostatic therapy would be avoided or reduced. In case the combination proves effective, it would improve the outcome of the disease and reduce toxicity, which would be a significant contribution to the treatment of such an aggressive subtype of breast cancer.

The aim

The aim of the study was to examine the disease outcome as the clinical benefit rate (CBR), progression-free survival (PFS), and overall survival (OS), both in the group of patients with HER2-positive metastatic breast cancer treated with systemic administration of trastuzumab with chemotherapy, as well as in patients with different status of hormone receptors HR+/HER2+ (ER+ and/or PR+/HER2+) compared to HR-/HER2+ (ER-/PR-/HER2+).

In addition, the study aimed to examine the differences in the disease outcome (PFS and OS) between patients with ER-positive receptors and ER-negative ones, as well as patients with PR-positive receptors and PR-negative ones.

Patients and methods

The study was conducted as a prospective observational study at the Oncology Clinic, Clinical Centre Niš. The study included 121 patients with pathohistologically verified HER2+ metastatic breast cancer treated with trastuzumab and chemotherapy during 2017 and monitored until June 2020.

The study involved patients with *de novo* diagnosed with HER2-positive metastatic breast cancer or with metastatic breast cancer after the disease-free interval of previously treated early or locally advanced breast cancer.

The inclusion criteria were as follows: patients ≥ 18 years, ECOG performance status 0-2 (12), not receiving chemotherapy or targeted molecular therapy for the treatment of metastatic disease, disease measurability according to RECIST 1.1. criteria (13), appropriate haematological and biochemical parameters, left ventricular ejection fraction (LVEF) > 50%. The exclusion criteria involved: metastatic spinal cord compression, symptomatic, untreated but actively progressive CNS metastases, rapid visceral progression, and severe cardiovascular disease.

Patients with metastatic breast cancer diagnosed after disease-free interval received:Paclitaxel at a dose of 175 mg/m^2 intravenously (i.v.) once in three weeks (3qw) or docetaxel at a dose of 80-100 mg/m^{2}i.v. once in three weeks, a total of 6-8 cycles concurrently with trastuzumab 600 mg subcutaneously (s.c.) once in three weeks. After the completion of chemotherapy, trastuzumab was administered at the same dose of 600 mg s.c. once in three weeks until the disease progression or unacceptable toxicity.

The following therapy was prescribed as premedication with paclitaxel: Amp.Dexason 20 mg i.v., Amp.Synopen 20 mg i.v., Amp.Ondasan 8 mg i.v., Amp.Bensedin 5 mg i.m.

The following therapy was prescribed as premedication with docetaxel a day before therapy, on the day of therapy, and a day after therapy: Dexason 8 mg in the morning and in the evening with Ranisan 150 mg in the morning and in the evening per os.

Patients with *de novo* diagnosed metastatic breast cancer first received anthracycline-based chemotherapy given that the indications of the Health Insurance Fund of the Republic of Serbia allow the use of trastuzumab as first-line treatment of HER2-positive metastatic breast cancer after the administration of anthracycline in combination with taxanes. This group of patients first received 4 cycles of chemotherapy according to the AC/EC protocol every 3 weeks (Doxorubicin 60 mg/m^2 or Epirubicin 90 mg/m^{2}i.v. day 1 in combination with Cyclophosphamide 600 mg/m^{2}i.v. day 1). The cycles are repeated every 3 weeks.

After the completion of anthracycline-based therapy, the above-described trastuzumab therapy in combination with taxanes was administered.

Before the onset of therapy, the cardiovascular status of each patient was assessed by echocardiographic examination with ejection fraction (EF) and ECG findings, and a complete blood test was done.

Statistical data processing

The data are presented in the form of the arithmetic mean and standard deviation, i.e. in the

form of absolute and relative numbers. The length of the overall survival (OS) and progression-free survival (PFS) was calculated and compared with parameters examined by the Kaplan-Meier curve and a log-rank test. The univariate Cox regression analysis was used to calculate the hazard ratio (HR) of the tested predictor variables. The hypothesis was tested with a significance threshold of $p < 0.05$. Statistical data processing was performed in the software package SPSS 16.0.

Progression-free survival (PFS) is defined as the time from the onset of the administration of systemic trastuzumab to disease progression or fatal outcome without disease progression.

Overall survival (OS) is defined as the time from the onset of the administration of systemic trastuzumab to fatal outcome caused by any reason, or last control check-up.

The clinical benefit rate (CBR) is the percentage of patients who achieved complete remission (CR) + partial remission (PR) + stable disease (SD).

It was necessary to make a record of the exact date of the first trastuzumab therapy, as well as the exact date of disease progression, fatal outcome (if occurred), or the last control follow-up.

Results

The study included 121 patients, mean age 55.45 ± 9.83 years (min 29 years, max 75 years). The majority of the examined subjects were in menopause - 82 subjects (67.8%), 23 subjects (19.0%) were not in menopause, whereas there was no data for 16 subjects (13.2%).

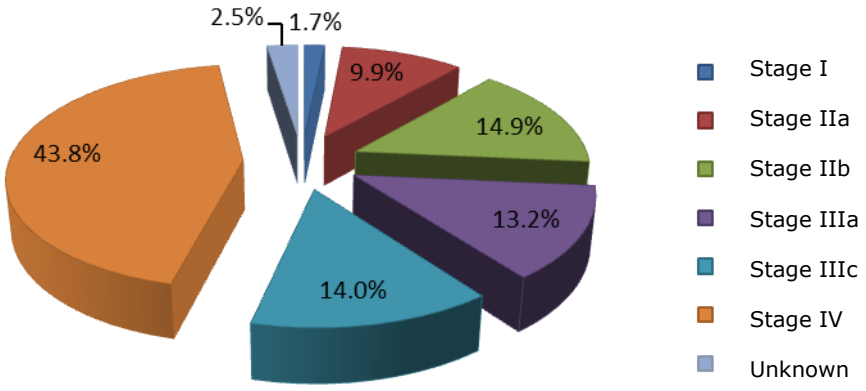
In most patients, HER2 was determined only from the primary tumor (86.8%). In less than 15.0% of the patients, HER2 was determined otherwise, from metastatic tumor biopsy samples or loco-regional recurrences (Table 1).

In the examined population, most patients were initially diagnosed in stage IV of the disease (43.8%), whereas 56.2% represented a relapse of previously treated breast cancer (Graph 1).

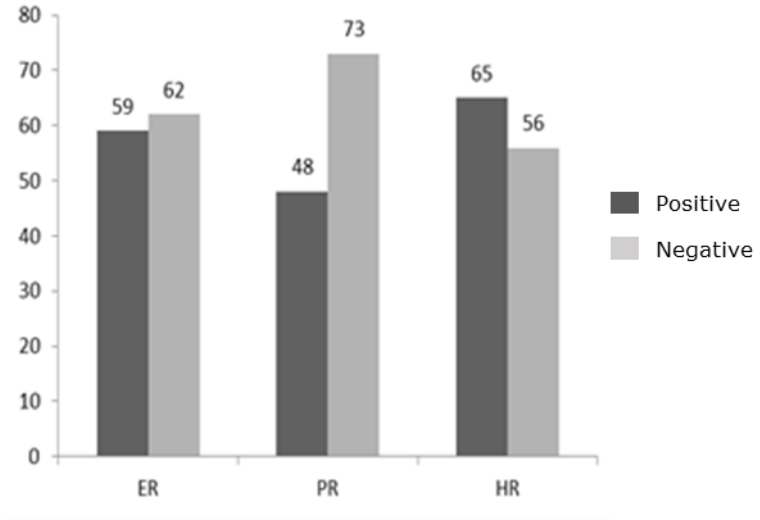
Fifty-nine patients (48.8%) had ER-positive receptors, and 48 patients (39.7%) had PR-positive receptors. Fifty-three point seven percent of the patients were HR-positive and 46.3% were HR-negative (Graph 2).

Table 1. Determination of HER2 status

HER2 determined from	Number	%
Primary tumor	105	86.8
Metastasis sample	1	0.8
Recurrence	5	4.1
Metachronous primary tumor	2	1.7
Primary tumor and metastasis sample	7	5.8
Primary tumor and recurrence	2	1.7
Total	121	100.0



Graph 1. The initial stage of the disease in the studied population



Graph 2. Distribution of ER, PR receptors and HR+/- in the studied population

Response to administered therapy

In the follow up period, most patients achieved partial remission of the disease (38.0%), followed by stable disease (31.4%), and disease progression (22.3%). Complete remission was achieved in less than 10.0% of the monitored population (8.3%). The clinical benefit rate was 77.7% (Table 2).

The distribution of the achieved response concerning HR- and HR+ was statistically signifi-cantly different (p = 0.005). Stable disease was found in 25.0% HR- and 36.9% HR+. Partial remission developed in 53.6% HR- and 24.6% HR+. Complete remission was present in 8.9% HR- and 7.7% HR+. (Table 3).

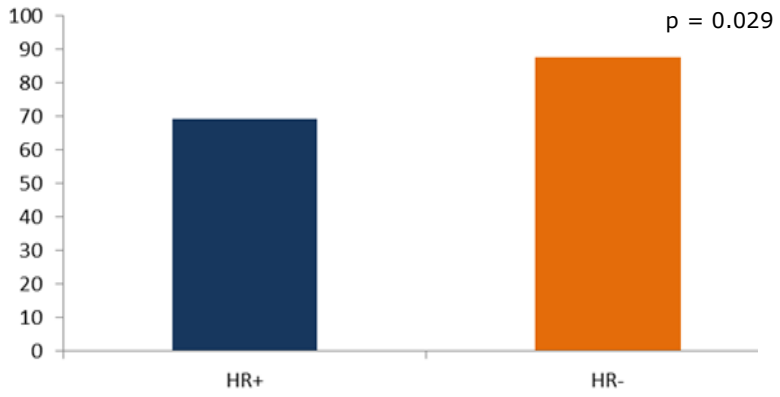
The clinical benefit rate was statistically significantly higher in patients with HR- compared to HR+ (p = 0.029). (Graph 3).

Table 2. Achieved response to administered therapy

Achieved response	Number	%
Stable disease	38	31.4
Partial remission	46	38.0
Disease progression	27	22.3
Complete remission	10	8.3
Total	121	100.0

Table 3. Achieved response regarding HR status

Achieved response	HR-		HR+		p
	n	%	n	%	
Stable disease	14	25.0	24	36.9	0.005
Partial remission	30	53.6	16	24.6	
Disease progression	7	12.5	20	30.8	
Complete remission	5	8.9	5	7.7	
Clinical benefit rate	49	87.5	45	69.2	0.029



Graph 3. Clinical benefit rate in HR+ and HR- patients

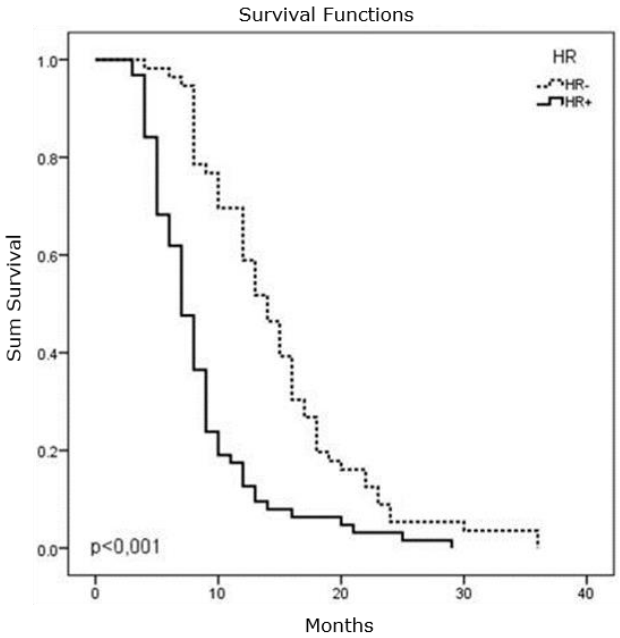
Treatment outcome - progression-free survival and overall survival

The average duration of the disease-free interval, progression-free survival and the overall survival in months is shown in Table 4.

The average time of the disease-free interval in the studied population was 11 months, and the mean duration of progression-free survival was statistically significantly different regarding the HR status. Patients with HR- have longer PFS compared to patients with HR+ (15 and 8 months, respectively). Patients with HR- tumors have a 62% lower risk of disease progression compared to HR+ tumors (HR 0.382; 95% CI 0.261-0.558, p < 0.001) (Graph 4).

Table 4. Disease-free interval, progression-free survival and overall survival in the studied population (in months)

Time (months)	AS ± SD	Min-Max
Disease-free interval	48.01 ± 21.57	19.00-134.00
Progression-free survival	11.36 ± 6.64	3.00-36.00
Overall survival	29.26 ± 12.63	6.00-66.00



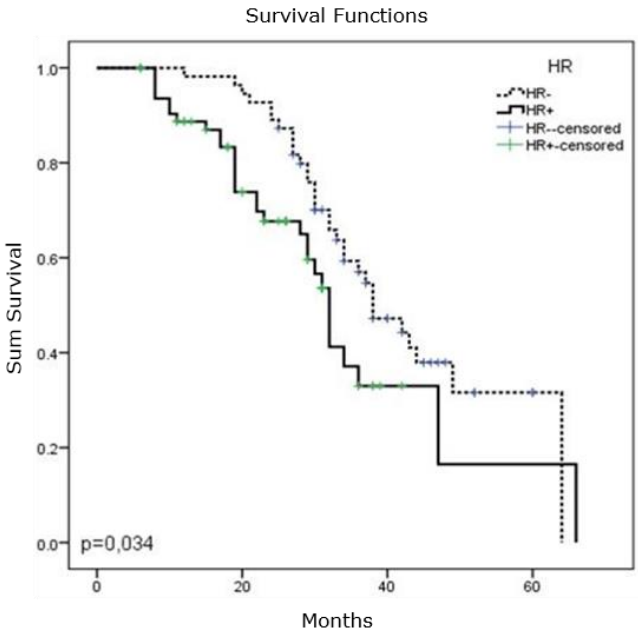
Graph 4. Kaplan-Meier curve of PFS regarding the HR status

Progression-free survival was statistically significantly different regarding the status of PR and ER receptors ($p < 0.001$ and $p < 0.001$, respectively). PR- have longer PFS compared to PR+ (13 and 8 months, respectively), i.e. they have a 59% lower risk of disease progression compared to PR+ receptors (HR 0.415; 95% CI 0.282-0.611, $p < 0.001$).

Estrogen receptor-negative tumors (ER-) have longer PFS compared to estrogen receptor positive ones (ER+) (14 and 9 months, respectively), i.e. a 56% lower risk of disease progression (HR 0.439; 95% CI 0.302-0.639, $p < 0.001$)

Overall survival was statistically significantly different regarding the HR status ($p = 0.034$). HR- patients have longer survival compared to HR+ patients (43 and 35 months, respectively). Hormone-insensitive tumors have a 43% lower risk of fatal outcome compared to hormone-sensitive tumors (HR 0.576; 95% CI 0.342-0.972, $p = 0.039$) (Graph 5).

In contrast to the duration of progression-free survival associated with the status of PR and ER, which was longer in ER- and PR-, no statistically significant difference in survival was found in ER+ ($p = 0.070$) or PR+ ($p = 0.291$) in comparison to negative receptors.



Graph 5. Kaplan-Meier curve of OS regarding the HR status

Discussion

After thorough processing and obtaining the results of this prospective study, the monoclonal antibody trastuzumab in combination with taxane-based chemotherapy has proved to be highly efficient and safe first-line therapy for metastatic HER2-positive breast cancer.

The aim of this study was to examine the disease outcome as the clinical benefit rate (CBR), progression-free survival (PFS) and overall survival (OS) in the entire group of patients with HER2-positive metastatic breast cancer treated with systemic administration of trastuzumab in combination with chemotherapy, as well as to examine differences in the disease outcome (CBR, PFS, and OS) between patients with different hormone receptor status HR+/HER2+ (ER+ and/or PR+/HER2+) versus HR-/HER2+ (ER-/PR-/HER2+). Given that a number of clinical studies have addressed this issue, our results will be compared primarily with two pivotal studies that introduced this combination of trastuzumab and taxanes into clinical practice, and afterward with smaller studies that examined the efficacy of this combination.

In the entire studied population, the overall response rate (ORR) was 46.3%, whereas the clinical benefit rate (CBR) was 77.7% with the highest percentage of partial remission (PR) - 38%, followed by stable disease (SD) - 31% and complete remission (CR) - 8%. This rate is slightly lower than in a pivotal study by Marty et al. which compared the efficacy of combining docetaxel with trastuzumab to trastuzumab alone. The results of this study showed that the ORR was 61% and the CBR was 88% in the combined group because the partial remission rate was 54%, which was higher than in our study, whereas the complete remission rate of 7% was comparable to our results (14).

When talking about the objective response rate (ORR), our results are also comparable to the results of a pivotal study by Slamon et al. which compared the efficacy of combining chemotherapy (paclitaxel or anthracycline) with trastuzumab to first-line paclitaxel alone in metastatic HER2-positive breast cancer. In their HO648g study, the ORR was 50% in the combined therapy group, whereas in the paclitaxel and trastuzumab group it was 42% with 8% CR and 34% PR, which is consistent with our results (5, 15). The results of these two pivotal studies incorporated the trastuzumab-taxane combination into clinical practice. They showed that PFS and OS were significantly longer in combination with trastuzumab compared to chemotherapy alone.

Progression-free survival was 11.7 months in the docetaxel group and 7 months in the paclitaxel group. Progression-free survival in our study amounted to 11 months, which is comparable, but also better compared to the results of pivotal trials.

Overall survival in the entire group of patients was 29 months, which is between the results of pivotal studies in which it amounted to 31 months in the docetaxel group and 25 months in the docetaxel with paclitaxel group. This result was expected given that our patients received both paclitaxel and docetaxel (5, 14, 15).

The main aim of our study was to examine the differences in the disease outcome (CBR, PFS, OS) between patients with different hormone receptor status HR+/HER2+ (ER+ and/or PR+/HER2+) compared to HR-/HER2+ (ER-/PR-/HER2+).

Resistance to trastuzumab has been intensively tested in recent years since it has been observed that not all HER2-positive cancers have the same benefit from anti-HER2 therapy. About 75% of breast cancers express ER and/or PR and belong to the group of hormone-sensitive cancers. About half of HER2-positive cancers express both ER and/or PR. *In vitro* and *in vivo* models suggest that there is a cross-talk of these two signalling pathways,which affects the response to therapy and treatment outcome of this group of patients.

It has recently been hypothesized that increased ER expression and/or activity may represent an avoidance mechanism or an alternative pathway leading to resistance to anti-HER2 therapy. For this reason, to realize the potential role of ER as one of the resistance mechanisms to trastuzumab, different HER2 positive breast cancer cell lines with *de novo* or acquired resistance to trastuzumab have been examined. It has been observed first in cell cultures that with constant inhibition of HER2 receptors, ER represents an alternative pathway by which HER2 positive cells proliferate and survive. In HR+/HER2+ cell lines in which the HER2 pathway was inhibited by lapatinib or the lapatinib/trastuzumab combination, resistance occurred via the ER signalling pathway which became the main promoter of cell growth and survival (8, 16). Other preclinical studies have shown that this response to anti-HER2 blockade is enhanced if fulvestrant hormonotherapy is added to lapatinib or trastuzumab (17). Studies on mice have shown that double blockade of HER2 and ER signalling pathways by different combinations of anti-HER2 and hormonotherapy (lapatinib, trastuzumab, pertuzumab, gefitinib, tamoxifen, aromatase inhibitors) induce the best response to therapy in HER2+/HR+ breast cancer (18-22).

Regarding metastatic HER2+ breast cancer, there is little data on the difference in the efficacy of anti-HER2 therapy in luminal and non-luminal tumors. However, these data, as well as the results of our study, suggest that ER or PR expression may be one of the mechanisms of trastuzumab resistance. In metastatic HER2+ breast cancer, no study that tested the efficacy of anti-HER2 therapy in combination with first-line chemotherapy was designed to add hormonotherapy to anti-HER2 therapy as maintenance therapy until disease progression after the discontinuation of chemotherapy in the group with luminal tumors.

For that reason, there are no clear clinical recommendations, but based on the presented findings, it is assumed that the blockade of both signalling pathways would be a good treatment strategy in this subgroup of patients.

In our population of studied patients, there were 65 (53.7%) HR-positive and 56 (46.3%) HR-negative patients. PFS was statistically significantly different regarding the HR status ($p < 0.001$). Patients with HR- had longer PFS compared to patients with HR+ (15 and 8 months, respectively). PFS statistically significantly differed regarding PR and ER receptors ($p < 0.001$ and $p < 0.001$, respectively). PR- patients had longer PFS compared to PR+ ones (13 and 8 months). ER- patients had longer PFS compared to ER+ ones (14 and 9 months, respectively). Overall survival was statistically significantly different concerning the HR status ($p = 0.034$). Patients with HR- had longer survival compared to patients with HR+ (43 and 35 months, respectively). Overall survival did not differ statistically significantly regarding PR ($p = 0.291$) and ER receptors ($p = 0.070$) alone.

Brufsky et al. conducted a retrospective analysis to record differences in treatment outcome in patients with HR-positive and HR-negative tumors in metastatic HER2-positive cancer treated with trastuzumab as monotherapy or in combination with chemotherapy. This analysis included patients from three clinical studies: the already described phase III of the pivotal study by Slamon et al. which showed the efficacy of the combination of paclitaxel with trastuzumab in first-line treatment (469 patients), then a study by Cobleigh et al. in which trastuzumab was tested as monotherapy in the second and third line of treatment (222 patients), as well as the phase II study in which trastuzumab was tested in the first line of treatment in standard and escalated doses with 114 patients. A total of 269 out of 596 patients (45%) had HR+/HER2+ tumors, whereas 255 out of 596 patients (43%) had HER2+/HR- tumors. In phase III pivotal study (H0648g), the ORR and TTP were similar in the trastuzumab and chemotherapy group for patients with HR+ and HR- tumors (ORR, 58% vs 51%; TTP, 7.6 vs 7.3 months, respectively). Overall survival was longer in the group with hormone-sensitive tumors (29.4 and 24.1 months, respectively) compared to the group with HR- tumors, which is contrary to our results. The hormone receptor status affected neither the

efficacy of trastuzumab as first-line monotherapy regarding the objective response to therapy (ORR 33% [95% CI, 20%-50%] vs 34% [95% CI 20.5% -50%] for HR-positive and HR-negative tumors, respectively) nor overall survival (OS 24.5 vs 20.5 months, for HR-positive and HR-negative tumors). The efficacy of trastuzumab in the second and third line of treatment was similar in terms of the hormone receptor status (5, 23-25).

Montemurro et al. conducted a retrospective analysis with 227 patients from 11 institutions treated with trastuzumab with chemotherapy in metastatic HER2-positive breast cancer. Out of a total of 227 patients, 49% had a hormone-sensitive tumor. High ER expression (more than 30% of cells) was associated with less benefit from the combination of trastuzumab and chemotherapy (HR 0.422; p = 0.009). In patients with HR+ tumors (1% of tumor cells), hormone therapy added to trastuzumab as maintenance therapy after the completion of chemotherapy was associated with significant benefit in PFS compared to cases in which it was not added (HR 0.521; 95% Cl, 0.3325-0.836; p = 0.007) (26). In our study, only 16 patients received hormone therapy as maintenance therapy and it was shown that the administration of hormone therapy in combination with trastuzumab in HR+ patients had a statistically significant effect on PFS (15 and 6 months, respectively, p < 0.001). So far, no study has been designed to confirm this concept, however, retrospective data, as well as data from preclinical and neoadjuvant and adjuvant treatment studies suggest the efficacy of this combination.

Another retrospective analysis was conducted on patients treated at the University Hospital in Italy (Udine) from January 2004 to July 2012 from all subtypes of metastatic breast cancer treated with multiple lines of therapy, i.e. a maximum of 4 lines. Patients with luminal A and HER2-positive tumors had the best prognosis. Regarding HER2-positive tumors, HR+ tumors had a better treatment outcome compared to HR-ones (OS: 55.3 and 26.0 months, respectively; PFS: 17.5 and 8.1 months, respectively). Patients with non-visceral bone metastases had a better treatment outcome in comparison to patients with liver or lung metastases (27). In our study, patients with visceral metastases had statistically significantly longer PFS compared to those with non-visceral metastases (p = 0.018), nevertheless, overall survival did not differ substantially (p = 0.638).

In the largest prospective observational study *registHER*carried out in the United States, a subanalysis was done on 530 patients (out of 1023) who were HER2-positive and HR-positive. Progression-free survival (PFS) and overall survival (OS) were the primary aim. HR+/HER2+ patients treated in the first line of metastatic breast cancer with the combination of trastuzumab and hormonotherapy had significantly longer PFS compared to those who received only hormonotherapy (13.8 and 4.8 months, respectively; HR 0.37, 95% CI: 0.22–0.60). Compared to patients treated with trastuzumab and chemotherapy in the first line of treatment, patients treated with trastuzumab with chemotherapy and hormonotherapy had longer PFS (20.4 and 9.5 months, respectively, HR:0.53, 95% CI:0.42–0.68) and a significantly lower risk of fatal outcome (HR:0.50, 95% CI:0.36-0.70). Sequential administration of chemotherapy with hormonotherapy showed greater benefit on overall survival compared to concurrent administration (HR:0.48, 95% CI:0.26 -0.89). The conclusion of this analysis, which actually reflects real world data, was that dual blockade of both ER and HER2 signalling pathways, with or without chemotherapy, was clearly associated with benefits in treatment outcome, i.e. longer PFS and OS compared to anti-HER2 therapy alone (28).

Conclusion

Based on the results of the conducted study in the entire group of patients with HER2-positive metastatic breast cancer treated with systemic trastuzumab with chemotherapy in the first line of treatment, it was concluded that the outcome of treatment (CBR, PFS, OS) was statistically significantly different regarding the HR status. Patients with HR- have longer PFS compared to patients with HR+ (15 and 8 months, respectively), as well as longer OS (43 and 35 months, respectively). Hormone-insensitive tumors have a 43% lower risk of fatal outcome compared to hormone-sensitive tumors (HR 0.576; 95% CI 0.342-0.972, p = 0.039).

Previous results indicate that results related to the influence of the hormone receptor status on the outcome of trastuzumab treatment in metastatic HER2-positive breast cancer are inconsistent. The question is whether the combination of anti-HER2 therapy with hormonotherapy without the administration of chemotherapy is a good treatment strategy. In metastatic HER2+ breast cancer, no study examining the efficacy of anti-HER2 therapy in combination with first-line chemotherapy has been designed so that after the discontinuation of chemotherapy, in the luminal tumor group, hormone therapy is added to anti-HER2 therapy as maintenance therapy to disease progression. Therefore, future clinical research should be focused in that direction.

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ESTROGEN RECEPTOR KAO MEHANIZAM REZISTENCIJE NA TRASTUZUMAB

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HER2 pozitivi hormonosenzitivni (HER2+/HR+) karcinomi od nedavno se izdvajaju kao poseban entitet. Postoji pretpostavka da povišena ekspresija i/ili aktivnost estrogen receptora (ER) može predstavljati mehanizam izbegavanja ili alternativni put koji dovodi do rezistencije na anti-HER2 terapiju.

Cilj rada bio je ispitati ishod bolesti kao stopu kliničke koristi (CCR – Clinical benefit rate), vreme do progresije bolesti (PFS) i ukupno preživljavanje (OS), kako u celoj grupi bolesnica sa HER2 pozitivnim metastatskim karcinomom dojke lečenih sistemskom primenom trastuzumaba uz hemioterapiju, tako i između bolesnica sa različitim statusom hormonskih receptora HR+/HER2+ (ER+ i/ili PR+/HER2+) u odnosu na HR-/HER2+ (ER-/PR-/HER2+).

Studijom je obuhvaćena 121 bolesnica sa patohistološki verifikovanim HER2+ metastatskim karcinomom dojke, koje su lečene tokom 2017. godine, primenom trastuzumaba sa hemioterapijom i praćene sve do juna 2020. godine.

Prosečna starost bolesnica bila je 55,45 godina ± 9,83 godine. HR pozitivno bilo je 53,7% bolesnica, a HR negativno 46,3% bolesnica. Vreme do progresije bolesti statistički se značajno razlikuje u odnosu na status HR. Bolesnice sa HR- imaju duži PFS u odnosu na bolesnice sa HR+ (15 meseci prema 8 meseci). Bolesnice sa HR- tumorima imaju za 62% niži rizik od progresije bolesti u odnosu na HR+ tumore (HR 0,382; 95%CI 0,261 — 0,558; p < 0,001). Ukupno preživaljavanje statistički se značajno razlikuje u odnosu na status HR (p = 0,034). Bolesnice sa HR- imaju duže preživljavanje u odnosu na bolesnice sa HR+ (43 meseca prema 35 meseci). Hormononesenzitivni tumori imaju za 43% manji rizik od smrti u odnosu na hormonosenzitivne tumore (HR 0,576; 95%CI 0,342 — 0,972; p = 0,039).

S obzirom na to da HR+/HER2− tumori imaju gori ishod lečenja trastuzumabom, buduća klinička ispitivanja bi trebalo da budu usmerena na kombinaciju hormonoterapije i anti-HER2 terapije kod ovog podtipa karcinoma.

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Ključne reči: *karcinom dojke, trastuzumab, rezistencija*