



Adjuvant application of trastuzumab in HER2 positive breast cancer and impact on time to relapse

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SUMMARY

Background: Of all breast cancers 20–25% are HER2 positive. Overexpression of HER2 protein on the surface of the malignant cell leads to excessive cell proliferation through different signaling pathways. Trastuzumab is a human monoclonal antibody that binds to domain IV of HER2 receptor and blocks signaling pathway for proliferation. The result is an improved prognosis for HER 2 positive breast cancer patients, even when compared to patients with other types of breast cancers. **Methods:** The study presents 74 women patients with early HER2 positive breast cancer who were previously operated (either radically or using breast conserving surgery), and received adjuvant chemo- and radiotherapy. Forty four patients received adjuvant trastuzumab for one year, and 30 patients did not (control group). Observed time to relapse of the disease was 60 months. **Results:** There was a significant difference in survival in favor of the group that received trastuzumab ($p < 0.001$). Application of trastuzumab also delayed relapse of the disease by 51.7%. No significant difference was observed between estrogen receptor positive and estrogen receptor negative cancers., In the control group there was a significant difference in relapse free survival in favor of estrogen and progesteron receptor positive tumors ($p < 0.001$). **Conclusion:** Survival of patients with a HER2 positive breast cancer whose prognosis was initially worse compared to HER2 negative patients, significantly improved after administration of trastuzumab.

Keywords: Cancer, Breast, Tyrosine kinase receptor, HER2, Trastuzumab, Prognosis, Antibodies

INTRODUCTION

Breast cancer is the most common malignant disease in women (1). It makes up about 26.5% of all newly discovered malignancies in the European female population and is responsible for 17.5% of the deaths. In males, this type of cancer is rare (one man per 100 women) (2). The frequency of the disease differs in various parts of the world. It is rarely seen before the age of 30, it rises with age and reaches its maximum around the age of 50 (3). The incidence of breast cancer in the world increases by 1–2% per year, and it is estimated that in the first decade of the third millennium, almost one million of women will suffer from breast cancer (4). However, in spite of the increasing possibilities of treatment, survival depends primarily on the extent and stage of the disease at the time of detection. In the early stage of the disease in which the largest number of patients is detected, healing is quite possible. Still, 24–30% of patients with lymph node negative and 50–60% with lymph node positive breast cancer will develop relapse. At the moment of diagnosis metastatic disease is present in 6–10% of patients (5).

Treatment of breast cancer is multidisciplinary. Combination of surgical treatment, radiation and systemic therapeutic treatment ensure good results in patient survival. The type and order of particular treatments must be planned multidisciplinary by surgeons-oncologists, radiotherapists and internists-oncologists (6). Clinical features of tumor such as size, the existence of tumor cells in the armpit lymph nodes, and distant metastases are considered essential in determining prognosis and choices of treatment. Prognostic factors, derived from breast tissue after biopsy or surgery, have significance in measuring tumor aggressiveness and general disease prognosis. The standard prognostic parameters are patient (menopausal status, age) and tumor related (tumor size, histological type, axillary lymphatic status, tumor gradient, ER, PR and HER2 status). Some

of them (ER, PR and HER2 status) have a predictive value because the best therapeutic modality is chosen based on these.

According to St. Gallen Consensus and ESMO recommendations from year 2013 breast cancers fall into different types according to histopathological findings and results of predictive and prognostic tests. Based on this, specific therapeutic approach is recommended. When luminal A type patient receive only endocrine therapy, and chemotherapy is considered only in cases of high risk tumor (with four or more positive lymph nodes, tumor size T3 or tumor grade 3). When luminal B-like type (HER2 negative) patient is treated using chemotherapy and endocrine therapy. When luminal B-like (HER2 positive) patient is treated using chemotherapy, anti-HER2 and endocrine therapy. In case of non-luminal (HER2 positive) breast cancer type chemo- and anti-HER2 therapy is recommended. In patients with basal-like (triple-negative) cancer application of chemotherapy is indicated (7).

HER2 oncoprotein (c-erbB-2)

The human epidermal growth factor receptor 2 (HER2) is a member of the epidermal growth factor receptor family. This oncoprotein is a transmembrane receptor which has similar or tandem functions with epidermal growth factor receptors. The hypersecretion of this protein is associated with increased growth and metastasis of tumor cells and with a shortened interval without signs of disease. Therefore, the determination of HER2 status is of prognostic significance (8).

HER2 is a 185-kDa surface membrane protein encoded by the c-erbB-2 gene that is found on chromosome 17q21. In breast cancer, the c-erbB-2 gene is amplified in approximately 20–25% of cases, so that instead of two copies, there may be up to 50 to 100 copies of the c-erbB-2 gene per cell (8, 9).

In everyday practice, level of HER2 is determined using immunohistochemistry and results are presented as: 0 (negative), 1+ (negative), 2+



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(when it is necessary to apply more sensitive methods - CISH or FISH) or 3+ (in this case HER2 overexpression is confirmed and these patients are candidates for administering trastuzumab). Trastuzumab is administered in an adjuvant, neoadjuvant and systemic treatment.

Trastuzumab is a humanized monoclonal antibody that is targeted against the extracellular domain of the HER2 transmembrane growth factor receptor. There are several mechanisms by which trastuzumab achieve a cytotoxic effect in HER2 positive breast cancer. One of cytotoxic effects of trastuzumab includes antibody-dependent cellular cytotoxicity (ADCC). Nagata et al. (10) reported that trastuzumab acts specifically on phosphatidylinositol 3-kinase (PI3K), increasing the level of phosphatase and tensin homolog (PTEN) protein in the cell membrane, that leads to inactivation of AKT serine/threonine protein kinases and inhibits cell proliferation (11). In addition, trastuzumab has antiangiogenic capacity (8, 10).

PATIENTS AND METHODS

The research design was a retrospective - prospective analytical study. The study was conducted at University of East Sarajevo, University Hospital Foča, Center for Internal Medicine, Department of Oncology, where chemotherapy was applied and regular patient check-ups were performed upon completion of treatment and University of Banja Luka, Clinical Center of Republika Srpska, Clinic for Oncology.

Group of 44 patients with HER2 positive breast cancer received monoclonal antibody therapy (trastuzumab) in adjuvant regimen. Group of 30 patients, with immunohistochemically confirmed (3+) HER2 breast cancer that did not receive monoclonal antibody therapy served as historical control (before monoclonal drug registration in the Republika of Srpska, Bosnia and Herzegovina). The follow up period was 60 months.

All patients were previously operated applying breast conserving surgery or radical mastectomy. The HER2 status was determined using immunohistochemistry and CISH (only in two cases when immunohistochemical HER2 status was 2+). All patients were investigated preoperatively for presence of metastases and it was confirmed that all were without secondary deposits (stage M0).

All patients received adjuvant chemotherapy both in the examined and control group. The most common was an anthracycline-based protocol (FAC) in 79.7% cases, followed by a combination of sequential anthracyclines and taxane (FAC + T) in 16.2%, and CMF protocol in 4.05% cases. Patients with positive hormone receptors received hormone therapy - 39.2% received adjuvant hormone therapy (tamoxifen), and only two patients received aromatase inhibitors (AIs).

Statistical analysis

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS, IBM; Version 20). Chi-square (χ^2) test, independent sample t test and Kaplan-Meier survival analysis were used to compare the data between the groups. Values were considered as statistically significant when $p < 0.05$.

RESULTS

A total number of 74 patients were analyzed. In the group that received trastuzumab there were 44 patients and 30 patients were in the control

group. The youngest patients were 26 (overall and examined group) and 34 (control group) years old. The oldest patients were 61 (control group) and 68 (overall and examined group) years old. Average age at the time of diagnosis was 47.3 (control group), 48.5 (overall) and 49.3 (examined group) years. Median age was 48.5 (control group), 49 (overall) and 49.5 (examined group). In all groups highest number of tumors was in T2 stage. Lower percentage of stage T1 and T3 tumors was observed. Highest number of tumors was in N1 (examined group) and N2 (control group) stage. A lower percentage of stage N0 and N3 tumors was observed (Table 1).

The most common type of breast cancer was ductal carcinoma (81.8%). Lobular carcinoma was present in 86.2% cases. Other histological types were absent. Histological second grade was the most common (65.9%), followed by third (20.5%) and first grade (11.6%) (Table 1). Highest number of tumors was of the nuclear grade II (68.5%), 16.4% were of the nuclear grade III and 15.1% of the nuclear grade I.

Characteristics	Examined group (n=44)	Control group (n=30)	Total (n=74)	P
Age, mean age (SD)	49.3 (9.2)	47.3 (8.2)	48.5 (8.8)	0.818 ¹
Size of the tumor, n (%)				
T1	7 (16.3)	3 (10)	10 (13.7)	0.730 ²
T2	30 (69.8)	23 (76.7)	53 (71.6)	
T3	6 (14)	4 (13.3)	10 (13.7)	
Lymph node status, n (%)				
N0	7 (15.9)	2 (6.7)	9 (12.2)	0.106 ²
N1	23 (52.3)	10 (33.3)	33 (44.6)	
N2	13 (29.5)	16 (53.3)	29 (39.2)	
N3	1 (2.3)	2 (6.7)	3 (4.1)	
Histological type of tumor, n (%)				
Ductal carcinoma	36 (81.8)	26 (86.7)	62 (83.8)	0.751 ²
Lobular carcinoma	8 (18.2)	4 (13.3)	12 (16.2)	
Histological grade of tumor, n (%)				
1	5 (11.6)	3 (10)	8 (11)	0.861 ²
2	29 (65.9)	22 (73.3)	51 (69.9)	
3	9 (20.5)	5 (16.7)	14 (19.2)	
Estrogen receptor status, n (%)				
Negative	29 (65.9)	17 (56.7)	46 (62.2)	0.470 ²
Positive	15 (34.1)	13 (43.3)	28 (37.8)	
Progesteron receptor status, n (%)				
Negative	30 (68.2)	18 (60)	48 (64.9)	0.620 ²
Positive	14 (31.8)	12 (40)	26 (35.1)	
Progression free survival, mean months (SD)	48.2 (2.1)	30.2 (2.7)	41.8 (1.9)	<0.001 ¹

n-number of patients, ¹ t-test(independent sample), ²Chi square test

Table 1. Patient's age, size of tumor, lymph node status, histological type and grade, estrogen and progesterone receptors and mean time to relapse

Estrogen and progesterone receptor (ER and PR) status

Of the 74 analyzed samples, 37.8% were estrogen positive, and 62.2% were estrogen negative. Progesterone receptors were negative in 64.9% and positive in 35.1% cases. (Table 1).

Majority of estrogen positive tumors were also progesterone receptor positive (78.6%, $p < 0.001$). In estrogen receptor negative tumors, the majority were with histological grades 2 (73.3%) and 3 (26.7%), while none were of histological grade 1. In estrogen receptor positive tumors, the highest number were with histological grades 2 (64.3%) and 1 (28.6%), and the lowest number were with grade 3 (7.1%). There was a statistical significance between estrogen receptor positive status and histological grade ($p < 0.001$) i.e. estrogen receptor negative tumors were of lower histological grade. Tumors with estrogen negative receptors were largely with nuclear grades II (75.6%), and III (22.2%). Tumors with estrogen positive receptors were in most cases with nuclear grade II (57.1%). There was a statistical significance between estrogen receptor negative status and higher nuclear grade ($p < 0.001$).

Time to relapse (Kaplan-Meier)

Probability of survival decreased with time in both examined and control group (Figure 1). The highest probability of survival was in the first 18 months of diagnosis, and then decreased.

Time to relapse and the probability of survival were significantly higher in the examined group compared to the control group.

Time to relapse (Kaplan-Meier) examined and control group

As it can be seen in Figure 2, there was a statistically significant difference in probability of survival between the examined and the control group (Log Rank = 21.801, $p < 0.001$).

In the examined group, relapse first appeared after 48.2 months, and in the control group after 30.2 months ($p < 0.001$) (Table 1). The latest relapse occurred in the examined group, after 56.6 months, and in the control after 40.9 months. The relapse free median survival time after 60 months of following up in the examined group was 52.4 months, and in the control group 35.6 months. In other words, 75% of patients in the examined group had no relapses, and in the control group 23.3%, which leads to a difference of 51.7%. Thus, the application of trastuzumab delayed the relapse of disease (PFS-progression free survival) by 51.7%.

Time to relapse in relation to the size of the tumor (T)

Comparing the tumor size in relation to the time to disease relapse, there was no statistically significant difference in the examined, not even in the control group.

Time to relapse in relation to the status of estrogen receptors (ER)

Analyzing the time to the occurrence of disease relapse according to estrogen receptor status, no statistically significant difference was found in the examined group, while in the control group there was a statistically significant difference in the sense that estrogen positive tumors had a lower probability of relapse compared to estrogen negative ($p < 0.001$) (Figures 3 and 4).

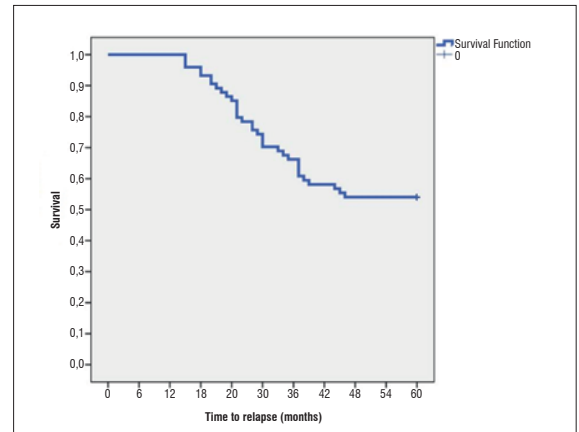


Figure 1. Kaplan-Meier analysis. Survival function

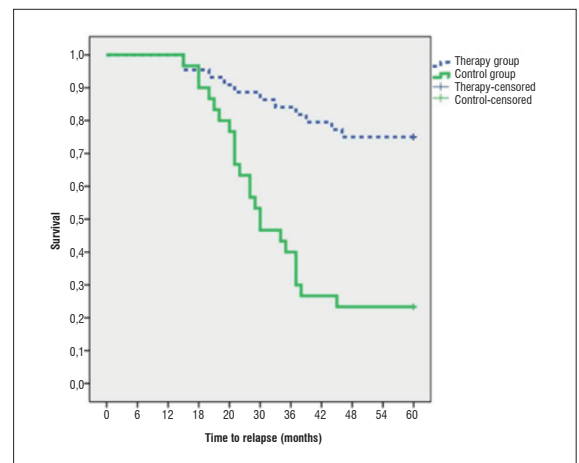


Figure 2. Kaplan-Meier analysis. By groups

Time to relapse in relation to the status of progesterone receptors (PR)

Analyzing the time to the occurrence of the disease relapse according to the status of progesterone receptors, no statistically significant difference was found in the examined group, whereas in the control group there was a statistically significant difference in the sense that progesterone positive tumors had a lower probability for relapse compared to progesterone negative ($p = 0.001$) (Figures 5 and 6).

DISCUSSION

The discovery of HER2 proto-oncogene and its role in the pathogenesis of breast cancer with development of anti-HER2 monoclonal antibody, trastuzumab (Herceptin), which blocks HER2 receptor, represents one of major discoveries in breast cancer treatment. Clinical trials in HER2 positive breast cancer patients have demonstrated that adjuvant application of trastuzumab with cytotoxic chemotherapy is associated with improved time to disease progression and overall survival (13). Our study also indicates that trastuzumab shows a significant overall survival benefit in early breast cancer over group with chemotherapy or radiation therapy. According to Kaplan-Meier curve, the relapse free survival time in both groups was highest in the first 18 months and then progressively declined until 48th month when it reached the plateau that persisted until the 60th month of follow-up.

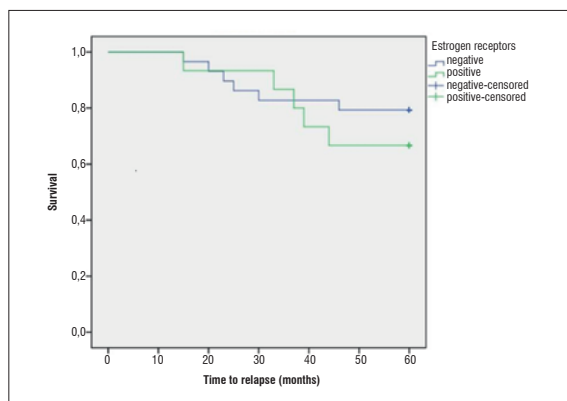


Figure 3. Kaplan-Meier analysis. By estrogen receptor status - therapy group

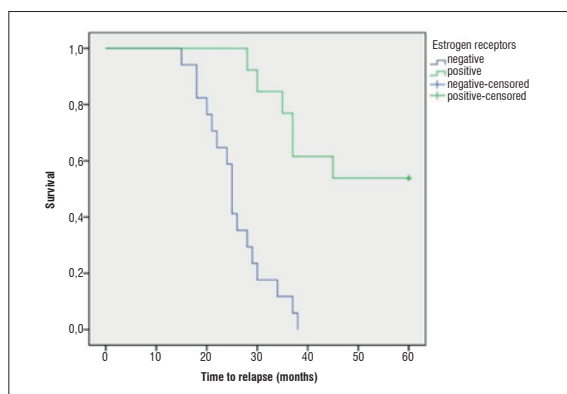


Figure 4. Kaplan-Meier analysis. By estrogen receptor status - control group

Analyzing the relapse free survival time by groups, there was a statistically significant difference in the survival between examined and control group (Log Rank = 21.801, $p < 0.001$). In the first 18 months of follow up there was no difference in survival between groups. Pivot et al. showed that out of 1691 patients who received trastuzumab in period of 12 months, and 1690 patients who received the same therapy in period of 6 months had similar survival rate. In this trial, two year disease-free survival was 93.8% (95% CI 92.6–94.9) in the 12-month group and 91.1% (89.7–92.4) in the 6-month group (hazard ratio 1.28, 95% CI 1.05–1.56; $p = 0.29$) (14). In our study, after 18 months period, the probability of survival decreased progressively more significantly in the control group compared to the examined group. Plateau in the examined group emerged about 48 months of follow up when the probability of survival was 0.8, and in the control group in 48 months a plateau of the curve was reached with probability of survival at 0.2. Analyzing relapse free survival within 60 months of follow up by processing of statistical data showed that in the examined group relapse was first noted after 48.2 months and in the control group after 30.2 months. The relapse occurred at the latest after 56.6 months in the examined group and after 40.9 months in the control group. In the study of Slamon et al. where 3222 women with HER2 positive early stage breast cancer patients were treated, it was shown that at a median follow up of 65 months, the estimated disease free survival rates at 5 years were 81% among those who received trastuzumab, and overall survival was 91% (15). In our study, the estimated mean relapse free survival time after 60 months was 52.42 months in the examined group, and 35.56 months in the control group. The difference in relapse free survival between

the examined and the control group was 51.7% for the benefit of the examined group. One of the largest and most recent meta-analyses that was focused on the adjuvant application of trastuzumab in HER2 positive early breast cancer patients incorporated six major randomized clinical trials with the longest follow-up periods and showed that intervention with trastuzumab had beneficial effects on disease free survival, overall survival and reduced risk of extracranial recurrence of disease (16). Similar results were also obtained in large registration studies for adjuvant trastuzumab - a significant reduction in the risk of the return of disease (HERA-46%, NSABP B31 and NCCTG N9831-52%, BCIRG 006-30 to 39%, Fin Her-58%) and significantly reduced risk of death (HERA-34%, NSABP B31 and NCCTG N9831-33%, BCIRG 006-34 to 41% and Fin Her for 59%) (17).

Analyzing the time until the occurrence of relapse according to estrogen receptor status, no statistically significant difference was found in the examined group, while in the control group there was a statistically significant difference in the sense that estrogen positive tumors had lower probability of relapses compared to estrogen negative tumors ($p < 0.001$). Results obtained in the control group are in accordance with data in literature where positive estrogen receptors are a prognostic parameter, for example, negative estrogen receptors are a predictor of worse prognosis, hence a higher probability for survival in estrogen positive tumors (18, 19).

The explanation of why there was no statistically significant difference in survival in the trastuzumab group between estrogen positive and estrogen negative tumors is the fact that in patients who had an expected worse

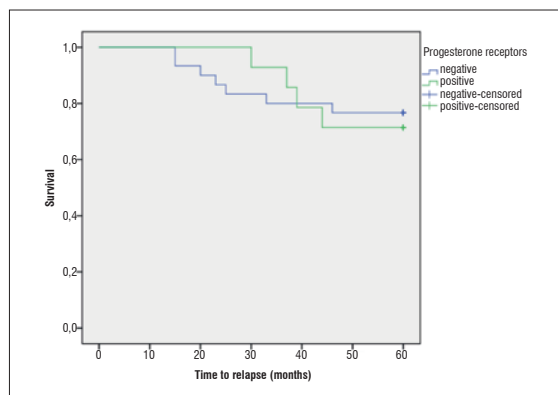


Figure 5. Kaplan-Meier analysis. By progesterone receptor status - therapy group

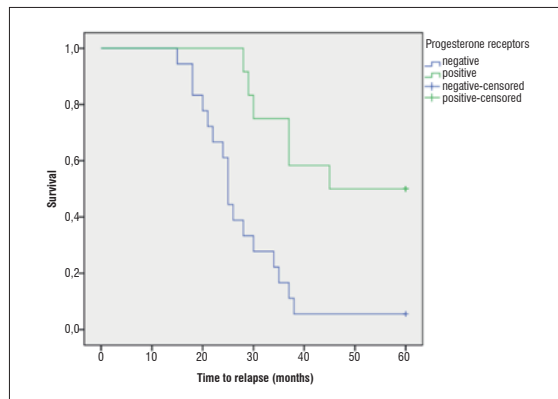


Figure 6. Kaplan-Meier analysis. Time to relapse by progesterone receptor status - control group

prognosis (ER negative, HER2 positive status), trastuzumab therapy was equalized with those with better prognosis (ER positive, HER2 positive status).

Analyzing the time to relapse according to the status of progesterone receptors, no statistically significant difference was found in the examined group, while in the control group there was a statistically significant difference in the sense that progesterone positive tumors had a lower probability of relapse compared to progesterone negative ($p < 0.001$).

Thus, in the control group, statistically significant difference in survival in favor of patients with progesterone positive tumors was expected and was consistent with literature data given that presence of progesterone receptors has a prognostic value i.e. they indicate better prognosis.

In the examined group there was no statistically significant difference in survival between progesterone positive and progesterone negative patients. Explanation for this is the same as previous (for estrogen receptor status) – it lies within the fact that trastuzumab therapy evened out survival of patients with different prognoses at the presentation.

However, it was shown that administration of trastuzumab produced numerous adverse events. The most severe toxicity resulting from trastuzumab treatment was cardiotoxicity that was expressed as a reduction in ejection fraction of the left ventricle by 10% or more or as cardiac decompensation (NYHA II and IV). These changes were reversible after termination of trastuzumab administration. Other side effects included fever, trembling, high temperature, muscle aches. They were rare and usually occurred after the first administration of the medicine (20, 21). In meta-analyses performed on randomized clinical trials by Viani et al. it was shown that cardiac dysfunction was the most common adverse event, occurring in 5% of treated patients. However, the same study showed that adjuvant application of trastuzumab showed significant reduction in mortality ($p < 0.00001$), recurrence ($p < 0.00001$), metastases rates ($p < 0.00001$) and formation of secondary tumors other than breast cancer ($p < 0.007$) compared to non-receiving patients (22).

CONCLUSION

Survival of patients with a HER2 positive breast cancer whose prognosis was initially worse compared to HER2 negative patients, significantly improved after administration of trastuzumab.

It can be said that discovery of HER2 receptor role and application of trastuzumab based therapy moved us a step forward to the oncology goal to approach the treatment of each tumor individually i.e. based on different biological characteristics of the tumor, we can apply personalized therapy with best therapeutic response.

Declaration of Interests

Authors declare no conflicts of interest.

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