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ORIGINAL ARTICLE

Ten years of using adjuvant trastuzumab in breast cancer in Serbia - Single institution experience

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Summary

Purpose: *The purpose of this study was to determinate disease-free interval (DFI) and overall survival (OS) in HER2-positive breast cancer patients who received adjuvant trastuzumab at the University Clinic of Nis, Serbia, and to investigate the influence of clinicopathological and biological characteristics of the tumor on prognosis. The second aim was to determinate the most frequent cause for the treatment discontinuation, recurrence rate, as well as the site of most common localization of the first recurrence of disease.*

Methods: *This research was conducted as a retrospective study at the University Oncology Clinic, Clinical Centre in Nis. The study included 238 patients who were operated and treated for HER2-positive breast cancer between January 1st, 2007 to September 30th, 2012 and followed up until December 31st, 2016. Trastuzumab was administered concurrently with taxanes, if administered, or after the completed anthracycline-based chemotherapy.*

Results: *After a median follow up of 69 months the 5-year DFI was 65.9% and 5-year OS was 81.8% and, as expected, significantly longer in the group of patients with smaller tumors, a smaller number of positive axillary lymph nodes, as well as a lower stage of disease (p<0.0001). Patients older than 65 years had a longer DFI compared to the 45-65 and under 45 age groups of patients (p=0.01). No statistical significance was found in the length of DFI in relation to the histological tumor subtype, tumor grade, or the status of hormone receptors. Unlike DFI, a longer OS was recorded in the group of patients with lower tumor grade (p=0.03) and there was no statistically significant difference in survival regarding the age of patients (p=0.07). Recurrence occurred in approximately one third of the patients (38.23%), mostly in the form of local recurrence. Adjuvant therapy with trastuzumab was not completely carried out in 18.49% of the patients, the most common reason being the progression of disease.*

Conclusions: *A long median follow up period of 69 months indicated that anti-HER2 monoclonal antibody trastuzumab, after anthracycline-based chemotherapy or concurrently with taxanes, is efficient and safe in treating early breast cancer.*

Key words: *adjuvant trastuzumab, disease free interval, overall survival*

Introduction

Breast cancer belongs to the group of moderately chemosensitive malignant tumors. Setting strict standards in the adjuvant therapy of breast cancer has led to the reduction of the risk of recurrence by administering hormone therapy in ER-positive breast cancer about 50%, administering trastuzumab in HER2-positive tumors by about 50%, and chemotherapy by about 15-40%, with a significant decrease in mortality [1].

Adjuvant trastuzumab following chemotherapy is accepted as the standard treatment in early BC since 2006, due to its favorable impact on the

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clinical outcomes. Adjuvant trastuzumab (Herceptin) was introduced in the treatment of early HER2-positive breast cancer (St. Gallen consensus conference) based on the results of large randomized clinical studies (HERA, NSABP B31, NCCTG N9831 and BCIRG 006), which included more than 13,000 women treated with adjuvant herceptin along with different adjuvant chemotherapy regimens [2-5].

Adjuvant herceptin reduces the risk of lethal outcome by 13.3% in the group of patients with high risk for recurrence (one life saved per 8 treated women), whereas the risk is reduced by 3.3% in the group of patients with low risk of recurrence (one life saved per 31 treated women). The introduction of adjuvant herceptin in the treatment of early breast cancer has made the biggest individual success in the recent decades [6]. According to the consensus, all patients with HER2-positive breast cancer should receive adjuvant herceptin, provided that they have a preserved function of the left ventricle (EF>50%). The exception includes patients with the most favorable prognosis (T<10 mm, N0) [7].

The aim of this study was to determine DFI and OS in HER2-positive breast cancer patients who received adjuvant trastuzumab at the University Clinic of Nis, Serbia, and to investigate the influence of clinicopathological and biological characteristics of the tumor on prognosis. The second aim was to determine the most frequent cause for the treatment discontinuation, recurrence rate, as well as the site of most common localization of the first recurrence of disease.

Methods

This research was conducted as a retrospective study at the University Oncology Clinic, Clinical Centre in Nis. The study included 238 patients who were operated and treated for HER2-positive breast cancer between January 1st, 2007 to September 30th, 2012 and followed up until December 31st, 2016. The patients were followed up from the start of chemotherapy to the end of 2016, or death.

HER2 is being routinely used in Serbia since 2007 and tumors were scored according to the intensity and completeness of cell membrane staining in 4 scores (0- no immunoreactivity, 1+: weak and incomplete membrane staining, 2+: borderline and 3+: strong and complete membrane staining). In case of HER2 2+ (borderline) chromogenic *in situ* hybridization (CISH) was performed. HER2 positivity was defined either by immunohistochemistry 3+ or 2+ with gene amplification detected by CISH.

Low risk patients (small tumors, up to 3 positive lymph nodes) received anthracycline-based chemotherapy: 6 cycles of FAC/FEC regimen every 3 weeks or 4 cycles of AC/EC regimen every 3 weeks [8,9]. High risk patients received anthracycline- and taxane-based chemotherapy: 4 cycles of AC/EC regimen followed by paclitaxel weekly (12 weeks) or 4 cycles of paclitaxel q3w or 4 cycles of AC/EC regimen followed by 4 cycles of docetaxel q3w or TAC regimen [8,10-12].

Trastuzumab was administered once every 3 weeks in a loading dose of 8 mg/kg, and then 6 mg/kg, or if applied once a week in a loading dose of 4 mg/kg, and then 2 mg/kg every week for one year. Trastuzumab was administered concurrently with taxanes, if administered, or after the completed anthracycline-based chemotherapy. Prior to trastuzumab therapy, as well as every 3 months during and 6 months after the last cycle, an echocardiogram with EF and FS was done.

Patients with hormone-sensitive tumors received one of the following hormonotherapies for 5 years or until recurrence of disease: tamoxifen 20 mg/day with/without ovarian suppression; anastrazol 1 mg/kg, letrozole 2.5 mg/kg, exemestane 25 mg/kg.

All patients with indicated postoperative radiotherapy underwent 3D conformal radiotherapy on ONCOR linear accelerator. The breast was irradiated from two fields with a tumor dose (TD) of 50 Gy in 25 fractions (5 weeks). In addition, in some cases, an additional boost of TD 10-16 Gy in 5-8 fractions was added to the tumor bed [13,14].

Statistics

The data obtained were entered in the database, in a table-like arrangement and shown in Figures. The primary aim included DFI and OS. The DFI was defined as the date of surgery to the first documented local or distant disease relapse. The OS was defined as the time from surgery to death from any cause, or to the date of the last follow up.

Survival curves were generated using the Kaplan-Meier method and log-rank test was used for comparison of survival between groups. The groups were designated with regard to tumor grade, ER and PR receptor status, initial stage of disease, patients' age at diagnosis, histological type of carcinoma, as well as lymph node involvement. Statistical significance was determined at $p<0.05$. All analyses were performed using the SPSS 17.0 software.

Results

The total number of patients included in the study was 238, with an average age of 52.53 years (range 25-80). Sixty patients (25.21%) were under 45 years, the largest number (159 patients; 66.80%) was in the 45-65 year group, and the lowest number of patients (i.e. only 19; 7.99%) was recorded in patients older than 65 years. Table 1 shows the patient and clinicopathological characteristics.

The treatments administered are shown in Table 2. Tamoxifen therapy was discontinued in two patients due to deep venous thrombosis (DVT), in one patient due to thromboembolism, and

in two patients due to endometrial hyperplasia and frequent curettage replaced with aromatase inhibitors.

Adjuvant therapy was not completely carried out in 44 patients (18.49%). The reasons of therapy discontinuation are shown in Table 3. The most common reason occurring in 25 (10.5%) patients was progression during adjuvant therapy with trastuzumab, followed by decline of ejection fraction in 3 (1.26%) patients.

Recurrence appeared in 91 patients (38.23%), and the most common sites are shown in Table 4. In most patients, the first site of recurrence was local, followed by the liver. The brain was the site of first recurrence in 7 patients (2.94%).

Table 1. Patient clinicopathological characteristics

Characteristics	*Patients, n (%)*
Histology	
Invasive ductal carcinoma	183 (76.89)
Inavsive lobular carcinoma	27 (11.34)
Other	28 (11.77)
Tumor size	
T1	91 (38.23)
T2	112 (47.05)
T3	16 (6.72)
T4	14 (5.88)
Unknown	5 (2.12)
Nodal status (pathological)	
N0	83 (34.87)
N1	67 (28.15)
N2	42 (17.65)
N3	43 (18.06)
Unknown	5 (1.27)
Number of lymph nodes removed Median (range)	13 (1-33)
Stage of disease	
I	47 (19.74)
II	90 (37.81)
III	98 (41.18)
Unknown	5 (1.27)
Grade	
G1	14 (5.88)
G2	129 (54.20)
G3	93 (39.07)
Unknown	2 (0.85)
Hormonal receptor status	
ER and/or PR positive	108 (45.76)
ER and PR negative	128 (54.24)
HER 2 positivity by	
IHH	199 (83.61)
CISH	39 (16.39)

ER: estrogen receptor, PR: progesterone receptor, IHH: immunohistochemical, CISH: chromogenic *in situ* hybridization

Table 2. Treatment methods

Treatment methods	*Patients, n (%)*
Surgery	
Breast conserving surgery	66 (27.73)
Modified radical mastectomy	172 (72.27)
Number of trastuzumab cycles received (range)	16 (2-18)
Adjuvant chemotherapy	
Anthracycline	182 (76.47)
Anthracycline/Taxanes	52 (21.85)
Taxanes	1 (0.42)
Other	3 (1.26)*
Adjuvant chemotherapy regimens	
AC/EC	28 (11.77)
FAC/FEC	156 (65.55)
AC+Paclitaxel/Docetaxel	46 (19.33)
TAC	5 (2.10)
CMF	3 (1.26)
Endocrine therapy	
Yes	99 (41.60)
No	139 (58.40)
Endocrine therapy	
Tamoxifen	56 (56.57)
Tamoxifen+OS/OA	5 (5.05)
Aromatase inhibitors	23 (23.23)
Tamoxifen/IA	15 (15.15)
Radiotherapy	
Yes	109 (45.80)
No	129 (54.20)

*3 patients received only CMF chemotherapy because of earlier myocardial infarction.
AC: doxorubicin/cyclophosphamide, EC: epirubicin/cyclophosphamide), FEC: 5 fluorouracil/epirubicin/cyclophosphamide, FAC: fluorouracil/doxorubicin/cyclophosphamide, TAC: taxotere/doxorubicin/cyclophosphamide), CMF: cyclophosphamide/5 fluorouracil/methotrexate, OS: ovarian suppression, OA: ovarian ablation, AI: aromatase inhibitors

Table 3. Objective reasons for postponement or interruption of trastuzumab therapy

Reasons	*Patients, n (%)*
Decline of EF	3 (1.26)
Progression during adjuvant therapy with trastuzumab	25 (10.5)
Incomplete documentation	2 (0.8)
Non-appearance of patient	4 (1.68)
Other	11 (4.62)
Own initiative	3
Toxic hepatitis	1
Allergic reaction	2
Myocardial infarction	2
CVI	1
Total arrhythmia	2

EF: ejection fraction, CVI: cerebrovascular insult

Table 4. The most common sites of first relapse

Sites	*Patients, n (%)*
Number of patients with relapse	91 (38.23)
Local recurrence	21 (8.82)
Contralateral breast	6 (2.52)
Ipsilateral axilla	4 (1.68)
Supraclavicular	6 (2.52)
Contralateral axilla	1 (0.42)
Lenticular metastases	3 (1.26)
Bone	15 (6.30)
Liver	18 (7.56)
Lung	13 (5.46)
Pleura	6 (2.52)
CNS	7 (2.94)
Ovary	1 (0.42)
Ascites	2 (0.84)

In 10 patients relapse was at the same time in two sites, and in 4 patients in 3 sites

Table 5. Hormone receptors and HER2 status change

Status changed	*Patients, n (%)*
HR positive→HR negative	7 (33.33)
HR negative→HR positive	2 (9.52)
HER2 positive→HER 2 negative	3 (14.29)
HER2 negative→HER 2 positive	0

HR positive: ER and/or PR+, HR negative: ER and PR negative

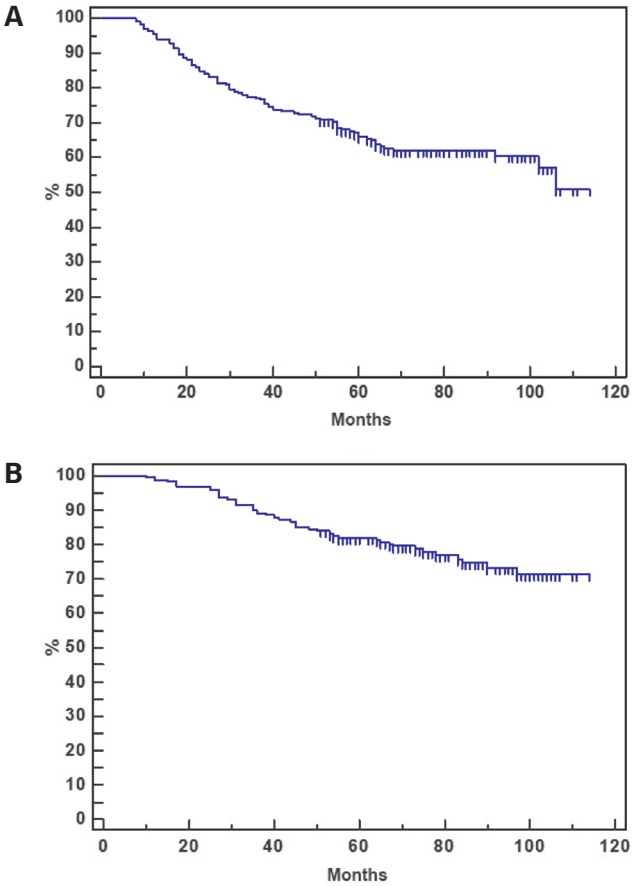

Figure 1. A: Disease-free interval. **B:** Overall survival.

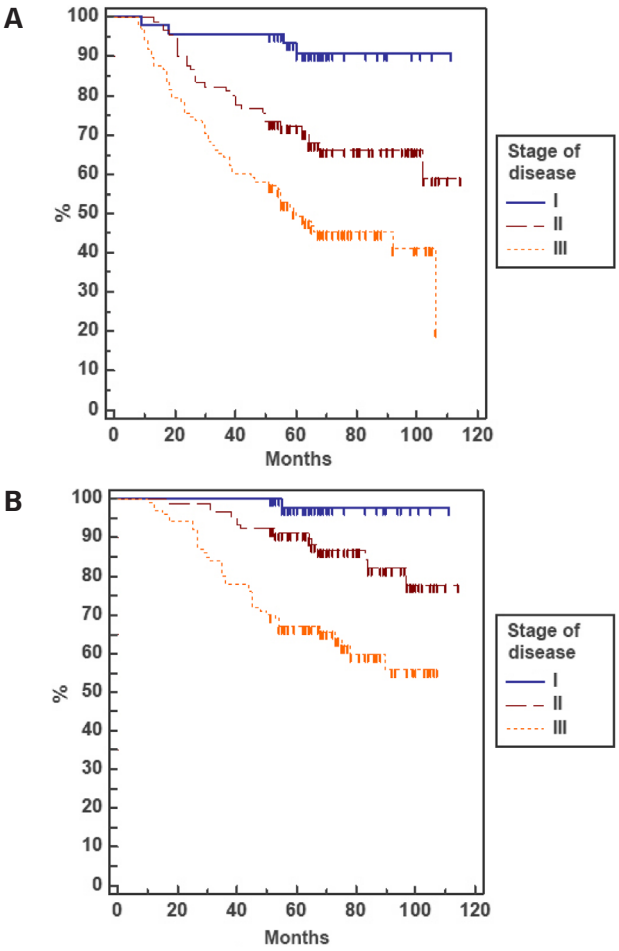

Figure 2. A: Disease-free interval according to stage of disease (p<0.0001). **B:** Overall survival according to stage of disease (p<0.0001).

Twenty one patients underwent surgery because of local recurrence (n=17) or contralateral breast cancer (n=4) and 12 out of these 21 patients experienced a change in estrogen receptor (ER), progesterone receptor (PR) or HER2 receptor status (57.14%), as shown in table 5.

The median time of follow up was 69 months.

Five-year DFI was 65.9% (Figure 1a) and, as expected, significantly longer in the group of patients with smaller tumors (p<0.0001), smaller number of positive lymph nodes (p<0.0001), as well as lower disease stage (p<0.0001, Figure 2a). Furthermore, patients older than 65 years had a longer DFI as compared to the 45-65 and under 45 years groups of patients (p=0.01, Figure 3a). No statistically significant difference was found in the length of DFI in relation to the histological tumor subtype (ductal vs lobular, p=0.12), tumor grade (p=0.29), or the status of hormone receptors (HR pos vs HR neg, p=0.71).

The 5-year OS was 81.8% (Figure 1b). As with 5-year DFI, OS was longer in the group of patients with smaller tumors (p<0.0001), less number of

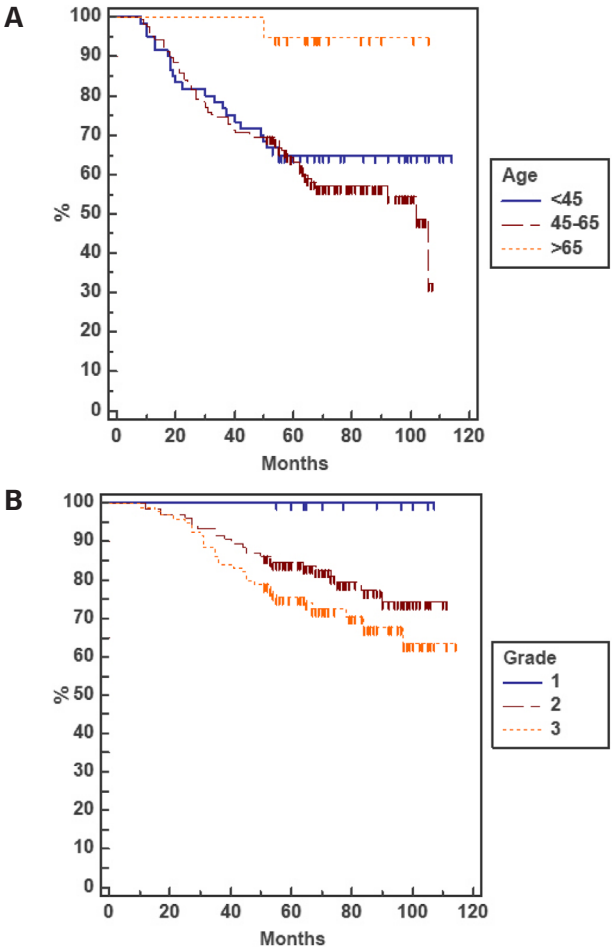

Figure 3. A: Disease-free interval according to patient age (p<0.01). **B:** Overall survival according to grade of tumor (p=0.03).

positive lymph nodes (p<0.0001), as well as lower stage of disease (p<0.0001, Figure 2b). Unlike DFI, longer survival was recorded in the group of patients with lower tumor grade (p=0.03, Figure 3b). The histological tumor subtype (p=0.73) or the status of hormone receptors (p=0.13) were of no significance. Moreover, unlike DFI, there was no statistically significant difference in OS regarding the age of patients (p=0.07).

Discussion

A long median follow up period of 69 months indicated that the anti-HER2 monoclonal antibody trastuzumab, after anthracycline-based chemotherapy or concurrently with taxanes, is efficient and safe in treating early breast cancer.

This study was limited due to the fact that there was a considerably large number of stage III tumors (41%), which would nowadays be candidates for neoadjuvant therapy. During the period when these patients were being treated, neoadjuvant therapy in Serbia, as well as in the rest of the world, had just started to be applied. Such a high percentage of stage III tumors was linked to the fact that the national screening for breast cancer began to be conducted in 2013, therefore the majority of patients had a tumor of 3-5 cm in size (47%).

Based on the results of four large randomized studies – HERA, NSABP B-31, NCCTG N9831 and BCIRG 006, which included more than 13,000 women with HER2-positive breast cancer, global regulatory bodies approved trastuzumab (herceptin) for a one-year-long treatment. To date, more than 1.2 million women receive this therapy [15-17].

The National Cancer Institute and the FDA approved a joint analysis of the results of two studies, NSABP B-31 and NCCTG N9831 [18]. In 2014, Perez et al. published the results after 8.4 years of follow up and showed that adding trastuzumab to standard therapy with anthracyclines and taxanes improved survival and reduced the risk of mortality by 37% (HR-0.63), as well as that DFI reduced the risk of recurrence by 40% (HR-0.60). Improvement was observed in all subgroups regardless of tumor size, hormone receptor status, lymph nodes status and age of patients [18]. The largest number of patients was between 40 and 60 years of age, and radical mastectomy was performed in the majority of them (60.9 and 62%, respectively), as it was in our study. About half of the tumors were T2 (50.6 and 53.6%, respectively for both studies), nodal status was mostly N1 (57.9 and 48.9%), whereas it was mostly N0 in our study (38.8%). We found almost an identical number of hormone-dependent tumors as Perez et al. (44.4 and 46.2%, respectively). In both studies, in trastuzumab groups, recurrence was reported in 11.9% of the patients, which was considerably less than in our study (38.2%). CNS as the site of the first relapse was reported in 3.1% of patients, and contralateral breast cancer in 2%, which was almost identical to the results of our study (2.94 and 2.5%, respectively).

The results of these two studies showed that a statistically much longer DFI was linked to patients with hormone-dependent tumors (HR-0.74, 95% CI 0.66 to 0.84, p<0.001), a smaller number of positive lymph nodes (p<0.001) and smaller tumors (p<0.001). Furthermore, OS in these subgroups was considerably longer (p<0.001), as well as in the ≥60 years group (p<0.001). Our study also showed that statistically much longer DFI was present in women with smaller tumors and a lower number of positive nodes (p<0.0001). Patients above 65 years of age had a significantly longer DFI (p<0.01), but there was no statistically signifi-

cant difference in survival regarding other groups. Also, patients in the low grade tumor group had a longer survival (p<0.03).

The 5-year OS in our study was 81.8%, whereas the 5-year DFI was 65.9%. The results of a mutual analysis of these two studies [18] published in 2014 showed that the 10-year DFI in the trastuzumab group was 73.7%, whereas the 10-year OS was 84%. Regarding DFI, our results are slightly worse than the results of Perez et al., but quite similar regarding the OS. In our study, OS in patients with N1, N2, and N3 status of lymph nodes was 85, 70 and 64%, respectively, whereas it was 89, 79 and 71%, respectively, in the joint analysis of these two studies. The present study showed that patients with hormone-independent tumors had a better survival, (84%), whereas the results of these studies showed the opposite [18].

The BCIRG 006 study is another study which examined the efficacy of adjuvant trastuzumab [19,20]. We found a lot of similarities with our study regarding the characteristics of patients and tumors. Radical mastectomy was performed in the majority of patients (63%), and the largest number of tumors was of T2 size (55%). The involvement of lymph nodes was mostly N1 (38%), and there were mainly hormone-dependent tumors (55%). After 5.4 years of follow up, the 5-year DFI and OS in group B (84 and 92%, respectively) were statistically longer compared to group A which did not receive trastuzumab (p<0.001). There were no statistically significant differences in DFI and OS between the two groups that received trastuzumab with different regimens. In the N0 patients, the 5-year DFI was 90% in those who received AC and docetaxel. In our study, node negative patients had a 5-year DFI of 81%. This study indicated that adding trastuzumab to chemotherapy also significantly improved DFI in the node positive group, especially with four or more positive lymph nodes (73%) [19]. In our study, DFI was somewhat lower - 59%.

We found that the 5-year DFI for tumors >1 cm and ≤2 cm was 85%, whereas the result of Slamon et al. [19] was similar – 87%. This group showed that adding trastuzumab to standard regimens had beneficial effects on OS and DFI in all subgroups. The percentage of patients who exhibited a decrease of EF by more than 10% ranged up to 18% in the trastuzumab and anthracycline group, whereas it was considerably smaller, below 2%, in our study.

There was a lot of controversy about the duration of trastuzumab administration and there are several studies which tested the efficacy of the administration shorter or longer than a year. The characteristics of patients included in our study were rather similar to the ones of patients from the HERA study. The number of patients under 35 years of age was 7%, and the greatest number of tumors was T2 (44%) and N0 (32%). The average age was somewhat lower, around 49, and the majority of tumors was of grade III (59%), compared with grade II in our study [21,22]. In 2013, after 8 years of monitoring, Goldhirsch et al. published the final results which showed that a year-long administration of trastuzumab remained the gold standard. Adding trastuzumab to standard therapy reduces the risk of recurrence by 24% (HR=0.76, p<0.0001) and the risk of fatal outcome by 24% (HR=0.76, p=0.0005) in comparison to chemotherapy without trastuzumab. The total number of recurrences was 23.6% in the group that received trastuzumab for a year, which was much lower than in our group of patients (38%), as well as the percentage of locoregional recurrences (5% HERA, 8.8% our study) [21,23]. There is some data that 9-week trastuzumab treatment was not inferior to 1-year trastuzumab treatment in early-stage, lymph node-negative breast cancer patients but was not confirmed by randomized clinical trials [24].

After 8 years of monitoring, cardiac events were present in only 1.9% in both groups receiving trastuzumab. Major symptomatic adverse cardiac events were rare and similar in both groups (0.8% and 1%) [23] (one-year trastuzumab, two-year trastuzumab). However, asymptomatic or minor adverse cardiac events, such as the decrease of EF, were higher in the group that received trastuzumab for two years (7.2%), compared to the group that received trastuzumab for one year (4.1%). In the HERA study, the efficacy of trastuzumab was equally significant regardless of the nodal status [21,23].

A subcutaneous (SC) formulation of trastuzumab which is administered once in 3 weeks for a year, has recently been approved for (neo) adjuvant therapy in HER2 positive early breast cancer [25-27]. To date it is proven that the SC formulation is preferred by patients and the nursing staff vs the IV administration [28]. All our patients are currently receiving the SC formulation, therefore, the results will be available in the near future.

Nowadays, there are ongoing trials with new anti-HER2 therapies. Having analyzed the results of the EXTENET study, the FDA has recently approved the registration of neratinib as a year-long adjuvant therapy after a year-long administration of trastuzumab. Furthermore, the registration of a dual blockade of trastuzumab with pertuzumab as adjuvant therapy is soon to be expected, after the results of the APHINITY study [29,30].

In conclusion the total population of the examined patients showed that adjuvant therapy with the anti-HER2 monoclonal antibody trastuzumab, after monochemotherapy with anthracyclines or in combination with taxanes, is efficient and safe in the treatment of early breast cancer. The 5-year DFI amounted to 65.9% and it was considerably longer in the group of patients with smaller tumors, less number of affected nodes, lower initial disease stage, as well as in those above 65 years of age. The 5-year OS amounted to 81.8%, it was considerably longer in the group of patients with smaller tumors, less number of affected nodes, lower initial disease stage, whereas age was of no significance. Recurrence occurred in approximately one third of patients (38.23%), mostly in the form of local recurrence. Adjuvant therapy with trastuzumab was not completely carried out in 18.49% of patients, the most common reason being the progression of disease.

Conflict of interests

The authors declare no conflict of interests.

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