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ORIGINAL ARTICLE

Trastuzumab 1-year vs 9-week in early-stage HER2-positive, lymph node negative breast cancer patients

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Summary

Purpose: *Optimal duration of adjuvant trastuzumab therapy in early-stage HER2-positive, lymph node-negative breast cancer is unknown. To establish this, we compared 1-year and 9-week trastuzumab regimens in HER2-positive, lymph node-negative early-stage breast cancer patients.*

Methods: *We retrospectively analyzed 4374 breast cancer patients. There were 181 early-stage, lymph node-negative breast cancer patients who were treated with adjuvant trastuzumab for either 9-week or 1-year schedule. A total of 101 patients received trastuzumab for 9 weeks and the remaining 80 patients received this adjuvant therapy for 1 year. Disease free survival (DFS) and overall survival (OS) rates of both groups were calculated.*

Results: *There was no difference between groups according to OS. Five-year OS rates were 95.5% in the 9-week group and 93.3% in the 1-year group (p=0.78). DFS was affected by age, having tamoxifen therapy and disease stage. Nine-week trastuzumab group was superior to 1-year group and 5-year DFS rates were 91% in 9-week group and 81.2 % in 1-year group (p=0.02). However, the 1-year group had more stage II patients than the 9-week group. We did not find any difference between groups regarding developing congestive heart failure.*

Conclusion: *It appeared that 9-week trastuzumab treatment was not inferior to 1-year trastuzumab treatment in early-stage, lymph node-negative breast cancer patients*

Key words: *adjuvant, breast cancer, trastuzumab, treatment duration.*

Introduction

Breast cancer is the most common malignancy in women and death rates related to breast cancer decrease due to new treatment modalities in the last 5 decades [1,2]. Human epidermal growth factor receptor-2 (HER2 or *HER2/neu*) is a gene playing significant role in breast cancer etiology and is found approximately in 25-30% of breast malignancies. New drugs targeting this gene have been used in the treatment of breast cancer patients [3-5]. Overexpression with/without amplification of the HER2 gene drives breast cancer cells to behave more aggressively [6,7]. HER2 gene overexpression is a negative prognostic factor in breast cancer patients and associated with aggressive tumor, angiogenesis, invasion and metastasis [8].

Trastuzumab is a monoclonal antibody targeting HER2 in breast cancer cells [9]. Adding trastuzumab to breast cancer treatment has led to significant improvements on DFS and OS in HER2 receptor-positive breast cancer patients given as adjuvant, neoadjuvant or in metastatic disease [4,10-14].

The clinical efficacy of trastuzumab, when it is used as a 1-year treatment in the adjuvant setting of HER2-positive breast cancer has been shown in several studies [15-17]. There is no objective criterion for 1-year trastuzumab administration in

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studies, and treatment duration is determined empirically. Therefore, the optimal treatment time of trastuzumab therapy is unknown and studies for determining optimal treatment duration are ongoing [18]. The FinHer study showed that adding 9-week trastuzumab to chemotherapy is an effective option in HER2-positive breast cancer patients [19].

Low cost, similar effectiveness, low cardiotoxicity, resistance to trastuzumab after 1 year treatment and provoking resistance to chemo and hormonotherapy are possible adverse findings and may drive physicians to a 9-week trastuzumab treatment [8,14-16,20]. After the FinHer study, physicians in our institute have given trastuzumab treatment as either 9-week or 1-year durations. Therefore, we compared 9-week vs 1-year trastuzumab treatment in terms of outcomes and toxicities.

Methods

Inclusion criteria and patient enrollement

After receiving local intuitional ethic committee approval, we retrospectively enrolled all patients who had adjuvant chemotherapy for HER2-positive, lymph node-negative breast cancer and only patients who received either 9-week or 1-year trastuzumab treatment were included. Patients who had neoadjuvant chemotherapy, patients with HER2-negative breast cancer, non-trastuzumab therapy regimens or trastuzumab regimens with duration other than 9-week or 1-year were excluded.

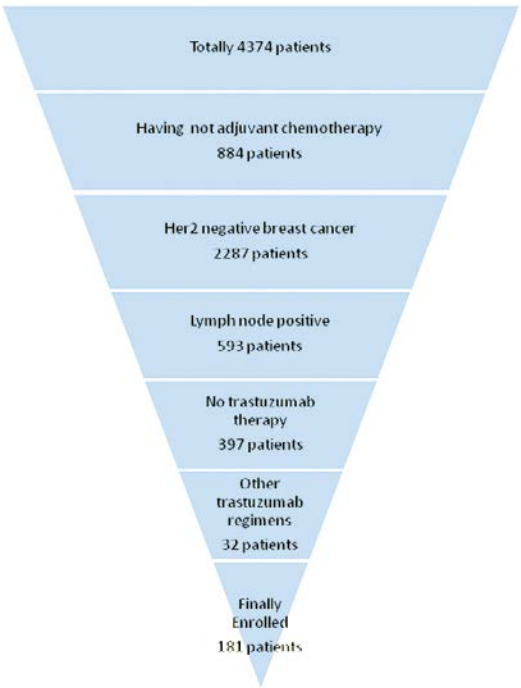

Figure 1. Patient enrollment.

From 1980 to 2015, 4374 patients were diagnosed with breast cancer in Hacettepe University Oncology Institute, Ankara, Turkey. Of these, 3490 (79.8%) patients were treated with adjuvant chemotherapy and 1203 (27.5%) had HER2-positive breast cancer. There were 610 patients who were lymph node-negative. Most of former patients did not have a chance for taking trastuzumab treatment and only 213 patients received trastuzumab. A further 32 patients were not enrolled in the study as they received trastuzumab regimens with duration other than 9-week or 1-year. Finally 181 patients between 2006 and 2015 fulfilled the enrollment criteria and were included in this study (Figure 1). The data were obtained from patients' hospital records as well as from the Turkish Ministry of Health cancer registry records.

HER-2 determination and trastuzumab therapy

Only HER2-positive patients were enrolled in the study. HER2 status was determined via immunohistochemistry (IHC) and fluorescent *in situ* hybridization (FISH) [4,21]. IHC 3+ or 2+ and FISH positive cases were accepted as HER2 positive [21]. Trastuzumab (Herceptin; Roche, Basel, Switzerland) was used as an adjunct to chemotherapy for HER2-positive breast cancer patients in the adjuvant setting [4,8,19].

Trastuzumab 4 mg/kg IV was given as initial dose followed by 2 mg/kg IV once a week in the 9-week group or 8 mg/kg IV as initial dose followed every 3 weeks at a dose of 6 mg/kg IV in the 1-year group [22]. Trastuzumab starting time changed according to patients' chemotherapy protocol and all patients finished their trastuzumab treatment. All patients were evaluated with echocardiography before and after trastuzumab therapy.

Hormonotherapy

Estrogen (ER) and progesterone receptor (PR) status was determined using the biopsy or surgical material before medical treatment and hormonotherapy was started. Hormonal treatment choice was determined regarding to patients' menopausal status, and hormone receptor-positive patients were administered anti-estrogen agents such as tamoxifen or aromatase inhibitors [23,24]. Tamoxifen was given 20 mg/day per os for 5 years [1,14,25]. Aromatase inhibitors were given only in postmenopausal patients [25]. Leuprolide and goserelin were also used for hormonotherapy [23].

Chemotherapy

Adjuvant chemotherapy regimens included anthracycline and taxane combination regimens, which consisted of 4 courses AC (adriamycin and cyclophosphamide) followed or not by 4 courses of paclitaxel; 4 courses of CAF (cyclophosphamide, adriamycin, 5-fluorouracil) followed or not by 4 courses of paclitaxel; 4 courses of TC (docetaxel and cyclophosphamide) or only 4 courses docetaxel or paclitaxel [24].

Surgery

The surgical treatment was either modified radical mastectomy (MRM) or breast conserving surgery (BCS) with radiotherapy. Surgical treatment choice was determined by patients' and surgeons' preference. The histopathology of breast tumors reported by our pathology department was categorized as ductal, lobular, tubular, medullary, mucinous and others [1,23]. All patients were also staged according to TNM staging system [1,23,24]. All patients were evaluated by clinicians for kidney and liver functions as well as cardiac functions via echocardiography before the start of chemotherapy and all included patients had normal organ functions.

Statistics

Numeric variables were presented as medians. Categorical variables were compared by the x2 test or Fisher's exact test. The non-parametric Mann-Whitney U test was used for non-categorical variables. OS and DFS were calculated from the date of breast cancer diagnosis. The distributions of OS and DFS durations in groups were estimated using the Kaplan-Meier method and compared using the log-rank test. No multivariate analyses of OS and DFS were performed due to less event count in patients. All reported p values were two-sided, and $p<0.05$ was considered significant. Statistical analyses were performed using SPSS 16.0 software.

Results

The median patient age at diagnosis was 49 years (range 23-82) and at menopause it was 48 (range 33-58). Of all patients 46% were pre-, 12% peri- and 42% post-menopausal. MRM was performed in 59% and BCS in 41% of the patients. Left-sided breast cancer was seen more often (61%) compared with cases with right-sided tumor (39%). ER-positive tumors were noted in 57% of cases and 52% of the lesions were PR-positive. Hormonotherapy was given to 62% of patients (data not shown).

The 9-week trastuzumab treatment group included 101 patients and the 1-year treatment group 80. Age at diagnosis, menarche and menopause, menopausal status at diagnosis, use of oral contraceptives and its duration, number of children, age at first pregnancy, breast feeding time, all comorbidities, tobacco use, previous history of cancer, cancer history in family, breast cancer history in family were similar in both groups (Table 1).

Breast cancer side, localization of the tumor in the breast, biopsy type, operation type, lymph node count, presence of vascular invasion, tumor

Table 1. Demographic features of patients

Features	*Trastuzumab 9 weeks, N (%)*	*Trastuzumab 1 year, N (%)*	*p value*
Age at diagnosis, years (range)	50 (23-82)	48 (26-70)	0.15
First menstruation age, years (range)	13 (11-16)	13 (11-16)	0.99
Menopause status			
Pre	41 (49)	42 (51)	0.2
Peri	15 (68)	7 (32)	
Post	45 (59)	31 (41)	
Age at menopause, years (range)	49 (33-58)	47 (38-55)	0.26
OC usage			
No	77 (58)	55 (42)	0.23
Yes	22 (48)	24 (52)	
OC years, months (range)	12 (1-180)	9 (1-180)	0.99
Delivery			
No	20 (59)	14 (41)	0.72
Yes	81 (56)	65 (44)	
Number of children	2 (0-5)	2 (0-7)	0.98
First birth, age (range)	21 (16-55)	23 (16-40)	0.12
Breastfeeding, months (range)	12 (0-48)	12 (0-36)	0.50
Comorbidity			
No	56 (51)	54 (49)	0.13
Yes	45 (63)	26 (37)	
Hypothyroidism			
No	83 (55)	68 (45)	0.61
Yes	18 (60)	12 (40)	
CAD or HT			
No	77 (55)	64 (45)	0.55
Yes	24 (60)	16 (40)	
DM			
No	89 (55)	74 (45)	0.33
Yes	12 (67)	6 (33)	
Tobacco use			
No	71 (55)	57 (45)	1.0
Yes	30 (57)	23 (43)	
Personal cancer history			
No	98 (55)	79 (45)	0.63
Yes	3 (75)	1 (25)	
Cancer in family			
No	34 (54)	29 (46)	0.76
Yes	67 (57)	51 (43)	
Breast cancer in family			
No	80 (58)	58 (42)	0.29
Yes	21 (49)	22 (51)	

CAD: coronary artery disease, DM: diabetes mellitus, HT: hypertension, OC: oral contraceptives.

Table 2. Disease characteristics

Characteristics	*Trastuzumab, 9 weeks, N (%)*	*Trastuzumab, 1 year, N (%)*	*p value*
Breast side			
Right	37 (52)	34 (48)	0.45
Left	64 (58)	46 (42)	
Cancer location			
Lower outer	17 (55)	14 (45)	0.25
Lower inner	9 (53)	8 (47)	
Upper outer	57 (63)	34 (37)	
Upper inner	14 (50)	14 (50)	
Areola	3 (33)	6 (67)	
Multiple	1 (20)	4 (80)	
Biopsy			
No	10 (56)	8 (44)	0.12
Excisional	27 (60)	18 (40)	
Incisional	14 (70)	6 (30)	
FNAB	12 (75)	4 (25)	
Trucut	38 (46)	44 (54)	
Surgery			
Breast conserving	43 (57)	32 (43)	0.76
MRM	58 (55)	48 (45)	
Histology			
IDC	99 (60)	67 (40)	0.001
ILC and mixed	2 (13)	13 (87)	
Lymph node count	10 (1-40)	10 (1-55)	0.30
Vascular invasion			
No	70 (56)	55 (44)	1.0
Yes	31 (55)	25 (45)	
Grade			
I	1 (50)	1 (50)	0.15
II	39 (66)	20 (34)	
III	61 (53)	54 (47)	
ER			
Negative	38 (49)	40 (51)	0.10
Positive	63 (61)	40 (39)	
ER%, mean (range)	80 (3-100)	80 (3-100)	0.73
PR			
Negative	45 (52)	42 (48)	0.30
Positive	56 (60)	38 (40)	
PR%, mean (range)	50 (1-100)	30 (1-90)	0.18
Her2 ICH			
2+	11 (61)	7 (39)	0.63
3+	90 (55)	73 (45)	
Tumor size			
T1	51 (67)	25 (33)	0.03
T2	42 (48)	45 (52)	
T3	8 (44)	10 (56)	
T1 size			
Mic	1 (100)	0 (0)	0.58
T1a	3 (75)	1 (25)	
T1b	6 (86)	1 (14)	
T1c	41 (64)	23 (36)	
TNM stage			
I	51 (67)	25 (33)	0.01
II	50 (48)	55 (52)	

ER: estrogen receptor, PR: progesterone receptor, FNAB: fine needle aspiration biopsy, ICH: immunohistochemistry, IDC: infiltrative ductal carcinoma, ILC: infiltrative lobular carcinoma, Mic: microscopic, MRM: modified radical mastectomy.

Table 3. Treatment of patients

	Trastuzumab 9 weeks, N (%)	*Trastuzumab 1 year, N (%)*	*p value*
Chemotherapy			
No	13 (93)	1 (7)	0.000
AC	71 (95)	4 (5)	
AC+Taxane	4 (18)	18 (82)	
CAF	7 (78)	2 (22)	
CAF+Taxane	0 (0)	3 (100)	
Taxane	2 (4)	46 (96)	
TC	4 (40)	6 (60)	
Taxane usage			
Only taxane	2 (4)	46 (96)	0.000
Chemotherapy w/wo taxane	86 (72)	33 (28)	
Adriamycin usage			
No	19 (26)	53 (74)	0.000
Yes	82 (75)	27 (25)	
Cyclophosphamide usage			
No	15 (24)	47 (76)	0.000
Yes	86 (72)	33 (28)	
5- Fluorouracil usage			
No	94 (56)	75 (44)	0.86
Yes	7 (58)	4 (42)	
Radiotherapy			
No	48 (55)	40 (45)	0.77
Yes	53 (57)	40 (43)	
Hormonotherapy			
No	34 (49)	35 (51)	0.17
Yes	67 (60)	45 (40)	
Tamoxifen usage			
No	61 (54)	53 (46)	0.44
Yes	40 (60)	27 (40)	
Serious cardiac adverse event			
No	96 (56)	76 (44)	1.0
Yes	5 (56)	4 (44)	

AC: adriamycin and cyclophosphamide, CAF: cyclophosphamide, adriamycin and 5- fluorouracil, TC: taxane and cyclophosphamide

grade, ER and PR status, HER2 IHC and T1 size were similar between the groups. Invasive lobular carcinoma and mixed histology were detected more frequently in the 1-year group than in the 9-week group. Stage 2 tumor and larger tumor size were detected more frequently in the 1-year group compared to that of 9-week group (Table 2).

Regarding the adjuvant treatment, the groups were similar in relation to using 5-fluorouracil containing regimen, radiotherapy, hormonotherapy, tamoxifen and treatment-related serious cardiac adverse events. However, chemotherapy protocols were different in groups. The 1-year group was more commonly treated with taxane only and the 9-week group was more frequently treated with AC (Table 3).

Table 4. Univariate analysis

	DFS			*OS*		
Variables	*2-year survival, mean±SE Months*	*5-year survival, mean±SE Months*	*p value*	*2-year survival, mean±SE Months*	*5-year survival, mean±SE Months*	*p value*
Age, years						
<50	91.5±3.3	82.8±5.1	0.049	98.7±1.3	91.2±4.4	0.23
≥50	98.8±1.2	95.9±3.1		100.0±0.0	100.0±0.0	
OC usage						
No	93.0±2.6	89.4±3.5	0.73	99.0±1.0	97.3±2.0	0.39
Yes	100.0±0.0	85.5±7.8		100.0±0.0	87.5±8.6	
Surgery						
Breast conserving	92.5±3.6	86.5±5.3	0.82	100.0±0.0	95.0±4.9	0.37
MRM	96.6±1.9	90.4±3.9		98.8±1.2	94.8±3.0	
Histology						
IDC	95.3±1.9	90.0±3.1	0.16	99.2±0.8	96.0±2.4	0.14
Others	88.9±10.5	74.1±16.1		100.0±0.0	85.7±13.2	
Comorbidity						
No	93.6±2.8	85.9±4.5	0.42	98.8±1.2	92.3±3.9	0.44
Yes	96.7±2.4	93.2±4.1		100.0±0.0	100.0±0.0	
Grade						
I	NA	NA	0.94	NA	NA	0.97
II	95.9±2.9	92.0±4.7		98.0±2.0	98.0±2.0	
III	95.2±2.4	87.3±4.4		100.0±0.0	93.2±3.9	
Stage						
I	100.0±0.0	96.7±3.3	0.005	100.0±0.0	100.0±0.0	0.35
II	90.6±3.4	82.8±4.9		98.7±1.3	92.0±4.0	
Menopausal status						
Pre	90.2±3.8	82.6±5.5	0.14	98.5±1.5	93.5±3.7	0.75
Peri	100.0±0.0	92.9±6.9		100.0±0.0	91.7±8.0	
Post	98.7±1.3	95.2±3.7		100.0±0.0	100.0±0.0	
Vascular invasion						
No	93.8±2.5	89.0±3.6	0.63	99.0±1.0	95.3±2.8	0.81
Yes	97.2±2.7	87.9±6.7		100.0±0.0	95.2±4.6	
Cancer in family						
No	95.2±3.3	91.4±4.9	0.88	100.0±0.0	96.3±3.6	0.59
Yes	94.6±2.4	87.4±4.1		98.9±1.1	94.8±3.1	
Breast cancer in family						
No	95.2±2.1	89.1±3.5	0.90	100.0±0.0	94.5±3.2	0.40
Yes	93.9±4.2	88.1±6.9		97.1±2.9	97.1±2.9	
ER						
Negative	92.7±3.6	89.6±4.6	0.95	100.0±0.0	100.0±0.0	0.31
Positive	96.3±2.1	88.3±4.3		98.8±1.2	91.8±4.2	
PR						
Negative	95.4±2.6	90.0±4.5	0.86	100.0±0.0	97.2±2.7	0.76
Positive	94.4±2.7	88.0±4.4		98.7±1.3	93.3±4.0	
HER2 ICH						
2+	93.8±6.1	93.8±6.1	0.81	93.8±6.1	93.8±6.1	0.67
3+	95.0±2.0	88.0±3.6		100.0±0.0	95.2±2.8	
Taxane usage						
Only taxane.	97.9±2.1	97.9±2.1	0.70	100.0±0.0	100.0±0.0	0.67
Chemotherapy w/wo taxane	94.6±2.1	88.0±3.5		99.1±0.9	94.7±2.7	
Adriamycin usage						
No	92.0±5.4	82.8±10.0	0.76	100.0±0.0	100.0±0.0	0.76
Yes	95.2±2.1	89.6±3.4		99.0±1.0	94.3±2.9	

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Cyclophosphamide usage						
No	NA	NA	0.14	NA	NA	0.47
Yes	93.8±2.3	87.2±3.6		99.1±0.9	94.7±2.7	
5- Fluorouracil usage						
No	94.4±2.1	88.6±3.4	0.59	99.2±0.8	95.6±2.6	0.62
Yes	100.0±0.0	90.9±8.7		100.0±0.0	90.9±8.7	
Radiotherapy						
No	95.7±2.5	90.0±4.6	0.72	98.5±1.5	95.6±3.2	0.54
Yes	94.2±2.8	87.6±4.5		100.0±0.0	94.7±3.8	
Hormonotherapy						
No	95.4±3.1	91.6±4.8	0.54	100.0±0.0	100.0±0.0	0.47
Yes	94.4±2.4	87.2±4.1		98.9±1.1	92.6±3.8	
Tamoxifen usage						
No	97.3±1.9	94.9±3.0	0.02*	100.0±0.0	100.0±0.0	0.10
Yes	91.2±3.8	80.8±5.9		98.2±1.8	89.4±5.2	
Trastuzumab usage						
9-week	97.0±1.7	91.0±3.3	0.02*	99.0±1.0	95.5±2.7	0.78
1-year	87.5±6.3	81.2±8.4		100.0±0.0	93.3±6.4	

ER: estrogen receptor, PR: progesterone receptor, ICH: immunohistochemistry, IDC: infiltrative ductal carcinoma, MRM: modified radical mastectomy, NA: not available, OC: oral contraceptive, RFS: relapse-free survival, DFS: disease-free survival, OS: overall survival, SE: standard error.

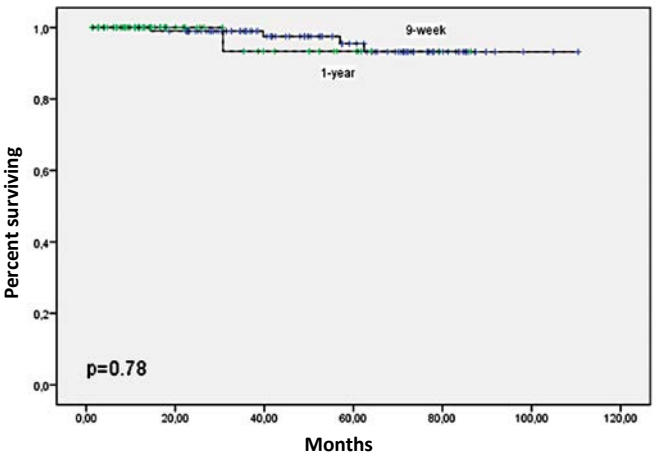

Figure 2. Overall survival of 9-week vs 1-year trastuzumab treatment.

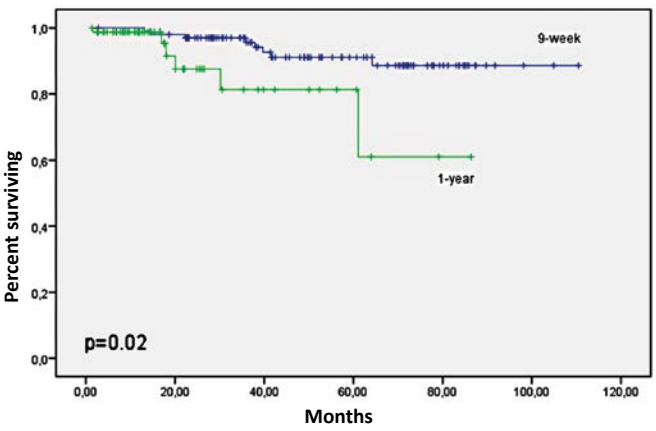

Figure 3. Disease free survival of 9-week vs 1-year trastuzumab treatment.

In univariate analysis the mean OS reached 106.6 months (±1.9 SE) in all patients but no variable affecting OS in all patients was detected (Table 4 and Figure 2). On the other hand, the mean DFS in all patients reached 99.4 months (±2.9 SE). Therefore young, stage 2, tamoxifen using and 1-year trastuzumab using patients had worse DFS (Table 4 and Figure 3).

Discussion

HERA, NSABP B-31, NCCTG N9831 and BCIRG 006 studies have evaluated the toxicity and efficacy of adjuvant trastuzumab [13,26-29]. In all these studies, patients not taking trastuzumab were compared with patients using trastuzumab. The above mentioned studies included more patients than our study and FinHer study and the duration of trastuzumab treatment in these studies were at least 1 year [13,19,26-29]. Although our research was conducted as a retrospective single-center study, the number of patients was close to the number of patients in FinHer study which was conducted as a prospective and multicenter trial. In FinHer study 232 of the patients were HER2-positive and 116 of them received 9-week trastuzumab, while the remaining 116 patients did not receive trastuzumab [19]. However, there was no comparison between 9-week and 1-year trastuzumab treatments in the FinHer study.

HERA trial showed that there was no extra benefit of 2-year trastuzumab compared to 1-year

[29]. PHARE trial reported that 1-year trastuzumab treatment should be the standard of care [30]. However, there was no difference between the 6-month and 1-year trastuzumab groups according to DFS in that study. In the TOG study, after a 3-year follow up, DFS rates were similar between the 9-week and 1-year trastuzumab groups [31]. The TOG study also showed that the DFS rates of 9-week and 1-year trastuzumab were similar in lymph node-positive early-stage patients. However, they did not compare the lymph node-negative patients.

Most of the patients were treated with MRM. While no significant survival advantage was shown between MRM and BCS, MRM is known to be better in terms of local disease control [23]. The information regarding the type of breast surgery was not given in the NSABP B-31, HERA, BCIRG 006, NCCTG N9831 and FinHer studies [13,19,26-29]. Besides, the operation type did not affect survival in the TOG study like in our study [31].

In our study, 61% of the patients were found to have cancer in the left breast. This coincides with the epidemiology of breast cancer that left breast cancer is seen more commonly [32]. This information, however, was not given in the NSABP B-31, HERA, BCIRG 006, NCCTG N9831, TOG and FinHer studies [13,19,26-29,31].

In the FinHer study, at the end of the 3- year follow-up, DFS was 89% and OS 96%. In the HERA study, the 3- year follow-up rates were 80% and 92%, respectively. In the BCIRG 006 study, these rates were 87% and 97%, respectively. In the NSABP B-31 and NCCTG N9831 studies, at the end of the follow-up period of 3 years, the DFS and OS rates were 87% and 94%, respectively. In the TOG study, the 3-year DFS rates were 88.6% and 85.6% in the 9-week and 1-year, respectively. In our study 5-year OS rates reached 95.5% in the 9-week group and 93.3% in the 1-year group. Therefore, 5-year DFS rates were 91.0% in the 9-week group and 81.2% in the 1-year group.

All of our patients had stage I and II disease, in addition to the fact that none of them had lymph node metastases. In the FinHer study, it was reported that the number of patients with positive lymph nodes was 89%. In the NCCTG N9831 and BCIRG 006 studies, all the patients were in the high-risk group and in NCCTG N9831 study no information on lymph node positivity was given. However, this rate has been reported 71% in the BCIRG 006 study. In the NSABP B-31 study all included patients had positive lymph nodes. Although the HERA study specified that patients were early-stage, there was no information regarding lymph node positivity. Therefore, in terms of lymph node positivity it is not possible to compare our study with HERA and NCCTG N9831 studies. The TOG study included lymph node-negative and lymph node-positive patients. The authors reported the lymph node negativity ratio as 42.6% in the 9-week group and 28% in the 1-year group. Due to the fact that lymph node positivity is the most important factor affecting the survival in breast cancer, patients in our study can be expected to have higher survival rates than other studies as they included more patients with positive lymph nodes [13,19,26-29,31].

In the present study, patients with ER-positive tumors were 57%, and PR-positive tumors 52%. Hormonotherapy was given to 62% of the patients. FinHER, NCCTG N9831, BCIRG 006, HERA, NSABP B-31 and TOG studies reported rates similar to our study. We think the hormone receptor status, due to very similar results, would not explain the higher survival rates in our study compared to others [13,19,26-29,31].

In hormonotherapy various resistance mechanisms are reported. Resistance to hormonotherapy is not just limited to tamoxifen. Development of resistance to HER2 would result in resistance to tamoxifen [14]. HER2 is known to have a role in letrozole-resistant breast cancer. HER2 protein was reported to be 6 times higher in letrozole-resistant tumors than in the control group [20]. There are common points of HER2 and ER signaling pathways. Estrogen regulates the expression of HER2 proto-oncogene. The pathway of HER2 may affect the sensitivity of anti-estrogen treatment in estrogen-dependent tumors. The TAnDEM study, which included patients with metastatic breast cancer, showed that the group receiving both trastuzumab and hormonotherapy had a superior DFS compared to the group receiving hormonotherapy only. Therefore, in ER-positive and HER2-positive breast cancer patients, the combination of hormonotherapy and trastuzumab should be given [25]. Having tamoxifen was one of the worst factors affecting DFS in our study, probably due to the fact that these patients had more aggressive tumors. Therefore, the results of our study were encouraging in terms of giving trastuzumab and hormonal therapy together in breast cancer patients. Also, a short period of trastuzumab treatment, such as 9 weeks, may prevent developing resistance to trastuzumab and hormonotherapy compared to 1-year trastuzumab administration and this statement may explain why 1-year trastuzumab patients had higher DFS in our study. However, additional studies are needed to confirm this observation.

In the present study, different chemotherapy protocols were applied to patients. The most common chemotherapy protocol which was given to the 1-year trastuzumab patients was taxane only and to 9-week group was AC. In the FinHer study, CEF (cyclophosphamide, epirubicin, 5-fluorouracil)+docetaxel or CEF+vinorelbine chemotherapy were given to patients. In the NCCTG N9831 and NSABP B-31 study, AC+paclitaxel were given to all patients; AC+docetaxel or docetaxel+carboplatin were given in the BCIRG 006 study. HERA study reported that patients received adjuvant or neoadjuvant therapy; however no further information was given about chemotherapy regimens [13,19,26-29]. In our study the most common regimens were anthracycline with cyclophosphamide and 9-week trastuzumab or taxane alone with 1-year trastuzumab. This was compatible with the chemotherapy which was given in previous studies. Trastuzumab can be combined with several chemotherapeutic agents and may form a better synergism. Combination together with other anthracycline derivatives provides a higher survival advantage than non-anthracycline containing combinations. In randomized trials, it was shown that CAF and CEF (anthracycline-containing regimens) have outclassed classic CMF (cyclophosphamide, methotrexate, fluorouracil) treatment. Due to the fact that anthracyclines and taxanes are the most active agents in patients with metastatic breast cancer, anthracycline and taxane combination has been widely used in early-stage breast cancer [23]. Survival data of our patients was good and it has been thought that the reason for this could be that trastuzumab was given together with anthracyclines and/or taxanes [4,12,24]. The FinHer study which gave trastuzumab for 9 weeks was planned to administer docetaxel or vinorelbine as single agents in the adjuvant treatment of breast cancer to compare their safety and efficacy. In this study it was shown that 1-year and 9-week treatment with trastuzumab had similar effects. It was also shown that the group receiving docetaxel was superior than the group receiving vinorelbine. Nine-week trastuzumab therapy combined with docetaxel at the same time showed that the antitumor effect was increased with the synergy [19]. In our study, trastuzumab often was given with taxanes or anthracyclines which might have increased the efficacy of chemotherapy [16]. However, we did not find any survival advantage among the different chemotherapy regimens.

Cardiac toxicity is high when trastuzumab and anthracycline are used together which is quite common in metastatic disease [7,13,31,32]. However, in non-metastatic adjuvant treatment, trastuzumab-related cardiac toxicity is not common, it can be managed medically and is reversible [4,15]. While the most common side effect in patients treated with trastuzumab was cardiac toxicity, the incidence of serious heart failure of 1-year treatment was less than 4% [19,31]. The authors of the FinHer study reported no trastuzumab-related congestive heart failure in their series. The TOG study reported significant decrease of left ventricle ejection fraction only in the 1-year group. However, there was no significant effect on congestive heart failure. In the present study, there was no clinically evident cardiac toxicity observed in either group. Therefore, we did not find any advantage of 9-week trastuzumab regarding serious cardiac adverse events.

Only in the FinHer and TOG studies trastuzumab therapy was given as adjuvant for 9 weeks. On the other hand, 1-year trastuzumab therapy was given in other above-mentioned studies. Nine weeks of trastuzumab treatment has the advantage of less toxicity and may be more attractive economically. Prolonged use of trastuzumab would cause higher economical costs. In patients with HER2-positive breast cancer, trastuzumab therapy given for 1 year constitutes the highest part of the cost of adjuvant treatment [27]. Trastuzumab therapy is proven to be an effective treatment in breast cancer, however, due to its high cost this treatment is still not offered routinely in many countries [13,16].

Tumor grade is also another important factor in survival [23]. We also evaluated vascular invasion as a prognostic parameter but we did not find any significant difference in our population of grade and vascular invasion. Disease stage is the most important prognostic factor after lymph node status. We found that stage II patients had lower DFS than stage I patients. In our study the 1-year trastuzumab group included more stage II patients than the 9-week group.

Our study was not a randomized controlled study and there could have been selection bias. Physicians' choice of trastuzumab duration may be affected by the disease stage. Consequently, this may explain why 1-year trastuzumab patients had lower DFS than the 9-week group as their stage was higher. However, one can still speculate that 9-week trastuzumab is at least not inferior to 1-year in early-stage, lymph node-negative breast cancer.

Conclusion

One-year duration of adjuvant trastuzumab therapy reported in many studies has been taken as empirical experience. There is no established rationale when evaluating its huge cost. As a conclusion, 9-week trastuzumab therapy appeared to be a safe, effective and economically attractive treatment option in low risk lymph node-negative early-stage breast cancer patients and may have similar survival rates to 1-year trastuzumab treatment.

Conflict of interests

The authors declare no confict of interests.

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