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Assessment of The Efficacy of Trastuzumab as Adjuvant Chemotherapy in Correlation with Clinicopathological Features in Patients with Her/2neu Positive Breast Cancer Attending Suez Canal University Hospital

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ABSTRACT

Materials and Methods: Retrospectively, data was collected from patients with HER2- positive early stage breast cancer who were receiving adjuvant trastuzumab. Then analysis of clinicopathological features of 88 patients and their treatment outcome was done. **Results:** 61 patients received trastuzumab and 27 patients didn't receive it. In patients who received trastuzumab **(trastuzumab group)**, the median follow-up period was 24 months (8.0-40.0 months). Relapse-free survival (RFS) was 31.2 months (95% CI: 28.0-34.4) and overall survival (OS) was 34.9 months (95% CI: 32.3-37.5). The 3-year OS for all patients was 76.9% and RFS was 62.3%. **In non-trastuzumab group**: the median follow-up period was 26 months (8.0-40.0 months). They were followed up during the course of treatment and it was found that relapse-free survival (RFS) was 30.18 months (95% CI: 25.2-35.1) and overall survival (OS) was found to be 32.0 months (95% CI: 27.3-36.6). So, the 3-year OS for all patients was 59.8% and RFS was 48.3%. 13.1% of the patients in the trastuzumab group had an asymptomatic decrease in left ventricular ejection fraction by more than 10% which is discovered by the end of the treatment course. Data obtained from univariate analyses revealed that larger tumor size, positive nodal involvement, and positive estrogen receptor status were significantly associated ($p<0.05$) with RFS. Positive lymph node was identified as an independent prognostic factor with multivariate analyses of covariates displaying $p<0.05$ (HR=1.8, 95%CI 1.1 - 3, p=0.01).
Keywords: Breast Cancer, Trastuzumab, Her2neu, Survival analysis.

INTRODUCTION

By far, breast cancer is found to be the most common cancer and is the leading cause of cancer-related mortality in women worldwide. [(1)]

There are several factors which are important in choosing the treatment strategy including gene expression studies, which have identified different molecular subtypes of breast cancer including: luminal A, luminal B, epidermal growth factor receptor 2 (HER2) type and triple negative (basal-like type). Those subtypes are classified based on histopathological markers including estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) [(2)].

HER-2 positive disease has been identified in about 15-25% of women with early breast cancer and it is found to be associated with an aggressive course, a poor prognosis and a higher risk of recurrence after initial treatment [(3)]. The human epidermal growth factor receptor2 (HER2) gene encodes for a transmembrane tyrosine kinase receptor protein and it is found to have important predictive and prognostic values for invasive breast cancer [(2)] .Trastuzumab is a humanized monoclonal antibody which acts by targeting the extracellular domain of the transmembrane tyrosine kinase receptor HER2. When administrated with adjuvant chemotherapy, It has shown its the ability in reducing the risk of relapse and death in HER2-positive breast cancer patients [(4)]

The adjuvant trastuzumab (HERA) trial median follow-up period was 2 years and it showed that 1-year of adjuvant trastuzumab treatment improved rates of disease-free survival (DFS) significantly, and the benefit also still observed at 4-year and 8-year median follow-up period [(4)] . From 2006, adjuvant trastuzumab was accepted to be a standard treatment in patients with HER2 positive breast cancer [(2)]. About 2.8% to 3.3% of patients treated with trastuzumab developed cardiomyopathy, which is the most common side effect of trastuzumab. So, resting left ventricular ejection fraction (LVEF) is used to monitor heart function during and after the course of treatment [(5)].

A national study used trastuzumab after adjuvant chemotherapy in patients with HER2-positive breast cancer and revealed that disease-free survival at 3 years was better in the intervention group who received trastuzumab compared to the group who did not receive it (89% vs. 78%) [(6)]. An international study conducted based on real life use and effectiveness of adjuvant trastuzumab in patients with early breast cancer and revealed that 5-year disease-free survival was 80.7% in patients treated with trastuzumab versus 68.2% in patients not treated with it, and also rates of 5-year overall survival were 90.7% and 77.4% respectively [(7)].

Another study obtained clinicopathological data of patients with HER2 positive breast cancer and assessed the efficacy of the use of adjuvant trastuzumab and its side effects including cardiotoxicity revealed that 3-year overall survival for all patients was 92.0% and relapse-free survival was 79.6%. The rate of relapse during follow-up period was 14.3%. Trastuzumab-associated cardiotoxicity was found at the rate of 3.3% [(2)].

MATERIALS AND METHODS

Approval of the Ethical Committee of the Faculty of medicine, suez canal university has been obtained.

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In the period from June 2013 to December 2015, 521 patients with breast cancer presented to oncology department of Suez Canal University Hospital. 88 patients were her2-neu positive (16.8 % of all breast cancer patients) were investigated, 61 patients of them received adjuvant trastuzumab following surgery, radiotherapy and adjuvant chemotherapy as follows:

4 cycles FEC, then 4 cycles taxol/trastuzumab followed by trastuzumab alone for 1 year which is administrated every 3 weeks. 27 patients didn't receive trastuzumab and received adjuvant chemotherapy (6 cycles FEC).

Data recorded from patients included: demographic characteristics of the patients, their histopathological data, ER and PR status, type of surgery, site of first relapse, and the time of relapse, adjuvant chemotherapy and radiotherapy status.

Cardiotoxicity developed during the course of treatment was recorded by doing electrocardiogram and echocardiography for LVEF to all patients every 3 months to monitor their cardiac function. A decrease in LVEF of >10% from baseline or a decrease to an LVEF <50% at any time was considered to be a cardiotoxicity.

The first relapse events were defined as local, or distant when they occurred, respectively, in the same breast as the first tumor, or in another part of the body (brain, bone, liver, lung, lymph nodes, and other organs). Relapse free survival (RFS) was defined as time from diagnosis to local, regional, or distant relapse, or death from breast cancer. Overall survival was defined as the time from diagnosis to death or final evaluation in the clinic.

Statistical analysis

Statistical data were analyzed using SPSS statistical software (version 20). Kaplan–Meier analysis was used for survival analysis. Cox regression model was used to evaluate univariate and multivariate analyses. $P< 0.05$ value was considered statistically significant.

RESULTS

Table 1. Clinicopathological data of Her2 positive patients who received trastuzumab

		Trastuzumab group	
		Frequency	Percent (%)
Age	Less than 50 years	37	60.7
	50 years or more	24	39.3
Menopausal state	Premenopausal	37	60.7
	Post-menopausal	24	39.3
Pathology	Invasive ductal carcinoma	57	93.4
	Invasive lobular carcinoma	-	-
	Medullary carcinoma	4	6.6
Tumor size	T1	8	13.1
	T2	32	52.5
	T3	15	24.6
	T4	6	9.8
Nodal involvement	N0	14	23
	N1	12	19.7
	N2	18	29.5
	N3	17	27.9
Grade	Grade 2	53	86.9
	Grade 3	8	13.1
Stage	Stage I	4	6.6
	Stage IIA	12	19.7
	Stage IIB	8	13.1
	Stage IIIA	16	26.2
	Stage IIIB	4	6.6
	Stage IIIC	17	27.9
Hormonal receptor status	Estrogen receptor		
	Positive	27	44.3
	Negative	34	55.7
	Progesterone receptor		
	Positive	21	34.4
	Negative	40	65.6
Type of surgery	Mastectomy	51	83.6
	Lumpectomy	10	16.4
	Total	61	100

Table 2. Clinicopathological data of Her2 positive Patients who didn't receive trastuzumab

	Non-trastuzumab group	
	Frequency	Percent (%)
Age		
Less than 50 years	13	48.1
50 years or more	14	51.9
Menopausal state		
Premenopausal	14	51.9
Post-menopausal	13	48.1
Pathology		
Invasive ductal carcinoma	25	92.6
Invasive lobular carcinoma	2	7.4
Medullary carcinoma	-	-
Tumor size		
T1	6	22.2
T2	15	55.6
T3	3	11.1
T4	3	11.1
Nodal involvement		
N0	5	18.5
N1	7	25.9
N2	1	3.7
N3	14	51.9
Grade		
Grade 2	22	81.5
Grade 3	5	18.5
Stage		
Stage I	3	11.1
Stage IIA	4	14.8
Stage IIB	5	18.5
Stage IIIA	1	3.7
Stage IIIB	-	-
Stage IIIC	14	51.9
Hormonal receptor status		
Estrogen receptor		
Positive	16	59.3
Negative	11	40.7
Progesterone receptor		
Positive	14	51.9
Negative	13	48.1
Type of surgery		
Mastectomy	22	81.5
Lumpectomy	5	18.5
Total	27	100

Cardiotoxicity: 13.1% of the patients in the trastuzumab group had an asymptomatic decrease in LVEF by more than 10% which is discovered by the end of the treatment course, while 86.9% didn't develop cardiotoxicity.

Survival: In patients who received trastuzumab (trastuzumab group), the median follow-up was 24 months (8.0-40.0 months). Relapse-free survival (RFS) was 31.2 months (95% CI: 28.0-34.4) and overall survival (OS) was found to be 34.9 months (95% CI: 32.3-37.5). The 3-year OS for all patients was 76.9% and RFS was 62.3%. In non-trastuzumab group: the median follow-up was 26 months (8.0-40.0 months). They were followed up during the course of treatment and it was found that relapse-free survival (RFS) was 30.18 months (95% CI: 25.2-35.1) and overall survival (OS) was found to be 32.0 months (95% CI: 27.3-36.6). So, the 3-year OS for all patients was 59.8% and RFS was 48.3%.

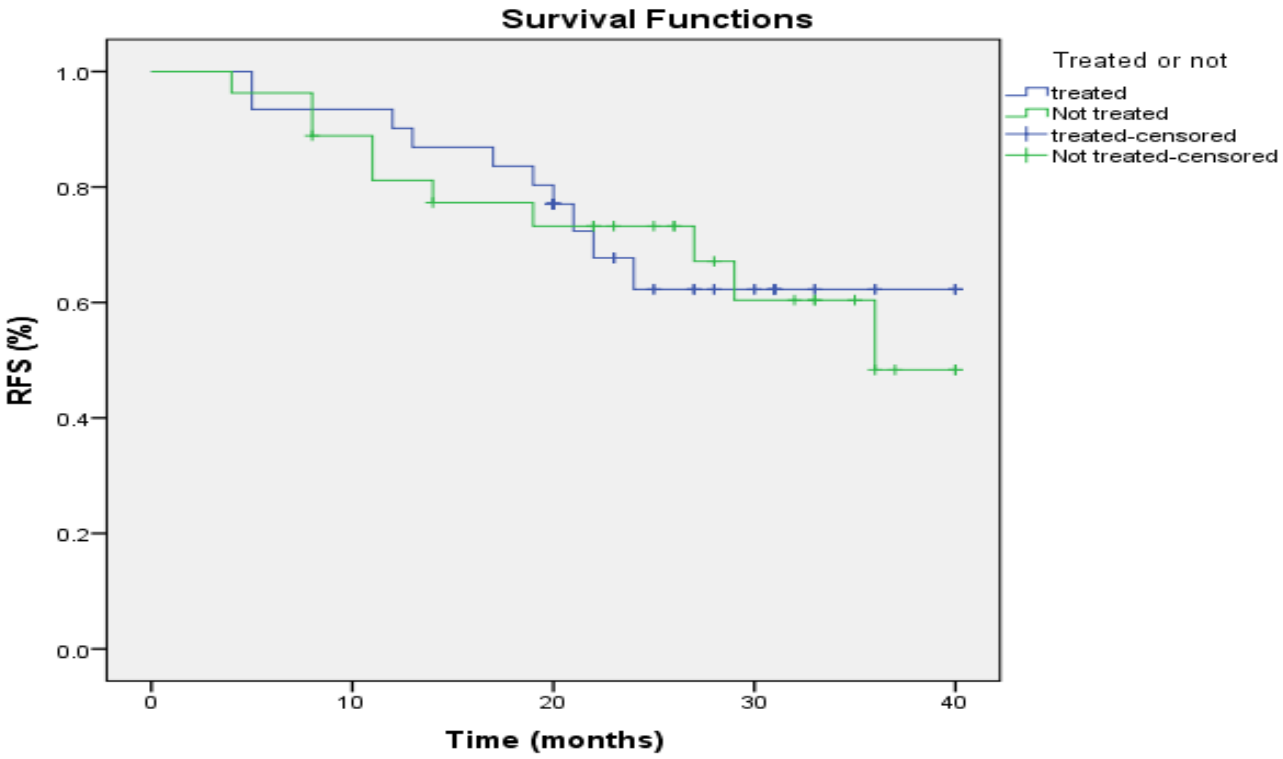

Figure 1. Relapse free survival for patients with her2- positive early breast cancer who received adjuvant trastuzumab and for patients who didn't

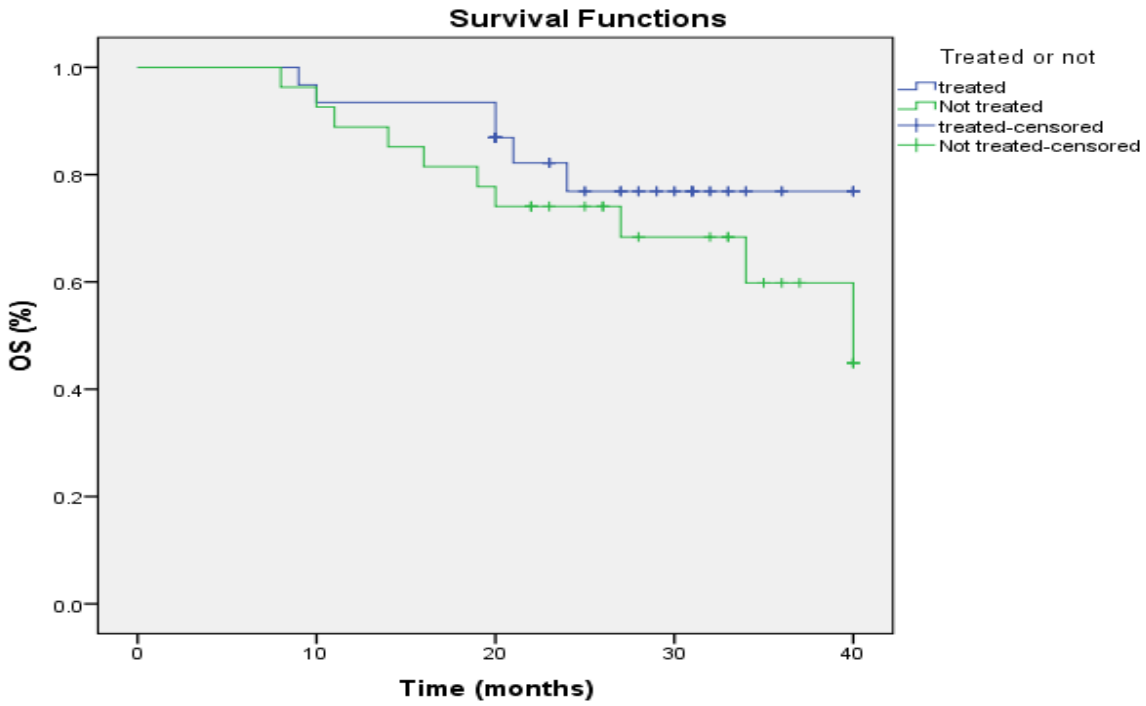

Figure 2. Overall survival for patients with her2- positive early breast cancer who received adjuvant trastuzumab and for patients who didn't.

Of the overall 61 patients who received trastuzumab, 51 completed planned adjuvant one-year trastuzumab treatment. Treatment was interrupted in 10 patients due to relapse during the treatment process.

In trastuzumab group: 3.3% of all patients developed local recurrence, while about 29.5% of the patients developed distant metastasis. 9.8% developed bone metastasis, there is a predominance of both liver and brain metastasis each represents 13.1% of all patients. No patients developed lung metastasis. In all patients, time to relapse ranged from 4 to 40 months with a median of 22 months. In non-trastuzumab group: 7.4% of all patients developed local recurrence, while about 29.6% of the patients developed distant metastasis. 22.2% of the patients developed bone metastasis, 18.5% developed lung metastasis, 14.8% developed liver metastasis and 7.4% of the patients developed brain metastasis. In all patients, time to relapse ranged from 4 to 40 months with a median of 26 months.

In the univariate analysis performed for RFS, no statistically significant relationship with age, menopausal status, surgical intervention, histopathology, tumor grade, progesterone receptor status. Data obtained from univariate analyses revealed that larger tumor size, positive nodal involvement, and positive estrogen receptor status were significantly associated ($p<0.05$) with RFS. Positive lymph node was identified as an independent prognostic factor with multivariate analyses of covariates displaying $p<0.05$ (HR=1.8, 95%CI 1.1 - 3, p=0.01) (Table 3).

Table 3: Univariate and multivariate analyses of parameters for relapse-free survival.

Parameters	Univariate analyses			Multivariate analyses		
	Hazard ratio	95%CI	P	HR	95% CI	P
Age (50 years or more vs. less than 50 years)	1.9	0.8-4.8	0.12			
Menopause (postmenopausal vs. premenopausal)	1.8	0.7-4.3	0.18			
Pathology (medullary vs. ductal carcinoma)	0.04	0.0-81.7	0.41			
Grade (III vs. II)	0.6	0.1-2.6	0.49			
Tumor size (>T1 vs. T1)	1.8	1.09-3.09	**0.02**	1.4	0.7-2.9	0.2
Lymph nodes (positive vs. negative)	2.07	1.2-3.3	**0.003**	1.8	1.1-3	**0.01**
Estrogen receptor (positive vs. negative)	2.7	1.0-7.1	**0.04**	1.7	0.5-5.2	0.3
Progesterone receptor (positive vs. negative)	1.5	0.6-3.8	0.3			
Surgery (mastectomy vs. conservative breast surgery)	1.9	0.4-8.3	0.3			

DISCUSSION

We conducted this study aiming to assess the efficacy of trastuzumab as adjuvant chemotherapy in correlation with clinicopathological features in patients with her/2neu positive early breast cancer attending clinical oncology department at Suez Canal University.

In this study, 61 patients out of 88 her2 positive breast cancer patients, received trastuzumab after surgery, radiotherapy and adjuvant chemotherapy. 27 patients didn't receive adjuvant trastuzumab. All patients were followed up in the period from 6-2013 to 12-2015.

During the period of follow-up, 16.8 % of all breast cancer patients were found to be Her2 positive and this matches the worldwide estimation of Her2 positive disease [3].

After data collection and performing the required statistical analysis, the presented study revealed that in trastuzumab group: more than half of the patients were less than 50 years old. This matches the HERA trial where more than half of her2 positive patients who received 1-year trastuzumab are less than 50 years old [8]

This also matches a study published in the New England Journal Of Medicine where also more than half of her2 positive patients included in the study were less than 50 years old [9].

In non-trastuzumab group: 51.9% of the patients were 50 years or more and this matches what is observed in a study of the Southeast Netherlands Breast Cancer Consortium [7].

In this study, in both groups (trastuzumab and non-trastuzumab groups): more than half of the patients were premenopausal, while in other studies including: an Asian study which conducted to evaluate clinicopathological features of early breast cancer patients with her2 positive[2], observational retrospective multicenter Italian study which assess the effect of adjuvant trastuzumab treatment in conventional clinical setting [4] and the HERA trial, most of the patients were postmenopausal.

This may be explained by the small sample size in this study. So, the study cannot be an indicator for the menopausal status of her2 positive breast cancer patients.

Most of the patients in both groups had invasive ductal carcinoma as expected with her2 positive carcinomas and this is compatible with the studies mentioned above [2,4].

More than half of the patients in the two groups had T2 carcinomas, 52.5% in trastuzumab group and 55.6% in non-trastuzumab group, and this is compatible with the data obtained from the HERA trial [8], where most of the patients had T2 tumors and also in some other studies [2,9–11].

In this study, only 23% of the patients in trastuzumab group, and 18.5% of the patients in non-trastuzumab group had negative lymph nodes while the rest were nodal positive and this matches the HERA trial [8], the combined joint analysis of (NCCTG) N9831 Intergroup trial and (NSABP) B-31 trial [12], and also other studies[2,4,9–11]. 86.9% of patients in trastuzumab group and 81.5% of patients in the non-trastuzumab group had grade 2 carcinomas, while rest of the patients had grade 3 tumors and this corresponds to only one study where most of the patients had grade 2 carcinomas [7].

But, it is different from other studies [10,11] and also the data obtained from the combined joint analysis of the North Central Cancer Treatment Group (NCCTG) N9831 Intergroup trial and National Surgical Adjuvant Breast and Bowel Project (NSABP) B-31 trial [12], where most of the patients had grade 3 carcinomas.

This difference may also be explained by the small sample size in our study which cannot represent the whole population.

In our study, stage III was the most common presentation in the patients in both groups and this is different from what is observed in one study [2], where stage II tumors were the most common among the study group. This difference may be due to small sample size in this study and also the late presentation of patients in the present study.We have found that 55.7% of patients in trastuzumab group were ER negative and this is not in the agreement with the results obtained from HERA trial [8], combined joint analysis [12], and other studies mentioned above [2,7,9,11] where more than half of the patients were ER positive.

This contradiction may be due to small sample size in this study which makes the results different from what is obtained worldwide.

In non-trastuzumab group: more than half of the patients (59.3%) were ER positive and this matches some other studies [7,11,12].

65.6% of patients in trastuzumab group were found to be PR negative and this is in the agreement with what is obtained from the combined joint analysis and other studies mentioned before [2,11,12], where also more than half of the patients were PR negative.

The opposite was seen in the non-trastuzumab group where 51.9% of the patients were found to be PR positive. This can be explained by the small number of patients in the non-trastuzumab group.

In our study, most of the patients in both groups underwent modified radical mastectomy and this is similar to the data from the joint analysis [12] and from other studies [2,7,9,10].

In the present study, relapses occurred within the first four months in both groups.

In trastuzumab group: distant metastasis occurred in about 29.5% of all patients. The most common sites of

metastasis were brain and liver followed by bone and no cases reported to have lung metastasis, while local recurrence developed in only 3.3% of the patients. Sites of distant metastasis, CNS involvement and recurrence pattern were nearly consistent with the findings of adjuvant studies [2,10].

In non-trastuzumab group: 7.4% of all patients developed local recurrence, while about 29.6% of the patients developed distant metastasis. The most common sites of metastasis were bone and lung followed by liver while only 7.4% of the patients developed brain metastasis. This is nearly consistent with the findings of previous research[10].

In patients with HER2 positive breast cancer, CNS disease is an important source of concern. In patients who received adjuvant trastuzumab, the first event was CNS metastasis while in those who do not receive this treatment, metastasis occurred in other sites earlier [11]. In metaanalyses performed, there was a significant increase in the risk of brain metastasis associated with trastuzumab treatment compared to patients who didn't receive it [13–15].

This can be explained by the ability of trastuzumab to control the systemic disease is stronger in areas other than CNS, and inadequate passage of trastuzumab from blood brain barrier [2,16].

As reported in four years follow-up results of the HERA trial, trastuzumab exerted the most beneficial effect in liver recurrences and percentage of liver metastasis was generally less than other types of metastasis [2,17]. This is against what is obtained in the present study where liver metastasis occurred in 13.1% of the patients. This difference can be explained by the small sample size in the present study and the short period of follow-up.

Conclusion: In the present study, trastuzumab was established to have treatment efficacy and satisfactory safety profile as in other clinical studies and that among clinicopathological factors evaluated, only positive lymph node involvement had a significant effect on RFS. However, with using adjuvant trastuzumab, there is high occurrence of recurrence which necessitates the need to identify molecular predictors, which will explain the resistance associated with anti HER2 based therapies.

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