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Targeted Treatment Trastuzumab is found to greatly Improve Long Term Survival of HER2 Breast Cancer Patients

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Abstract

The goal of this study is To assess the importance of adding adjuvant TRASTUZUMAB as a standard in her2 over expressed breast cancer. Fifty female patients have known to be HER2 over expressed breast cancer, recruited from clinical oncology clinic at Beni-Suef University hospital and from the insurance hospital at Beni-Suef city. This is retrospective study. This study was done within a six months. The results of this trial indicate that one year of adjuvant trastuzumab should be considered a standard on completion of loco regional therapy and neoadjuvant or adjuvant chemotherapy. That study indicated that adding trastuzumab to chemotherapy had improved overall survival &disease free survival, all the recruited patients in that study were still alive till the end of the study and about 8% (n=4) vs 92% (n=46) of patients developed distant recurrences. Receiving adjuvant TRASTUZUMAB for 1year without delaying in initiation (≤ 6 months) after diagnosis, offers dramatic effects on overall survival OS and disease free survival DFS.

Keywords: Disease free survival (DFS), Overall survival (OS), Neoadjuvant chemotherapy.

of physical exercise, drinking alcohol, hormone replacement therapy during menopause, ionizing radiation, early age at first menstruation, having children late or not at all, older age, and family history. About 5–10% of cases are due to genes inherited from a person's parents, including BRCA1 and BRCA2 among others. Breast cancer most commonly develops in cells from the lining of milk ducts and the lobules. In addition, there are more than 18

1. Introduction

Breast cancer is the most common cancer worldwide. Signs of breast cancer may include a lump in the breast, a change in breast shape, dimpling of the skin, fluid coming from the nipple, or a red scaly patch of skin. In those with distant spread of the disease, there may be bone pain, swollen lymph nodes, or shortness of breath *[1]*. Risk factors for developing breast cancer include: female sex, obesity, lack

cell, and turn genes on and off. The HER protein, Human Epidermal Growth Factor Receptor, binds to Human Epidermal Growth Factor, and stimulates cell proliferation. In some cancers, notably certain types of breast cancer, HER2 is over-expressed, and causes cancer cells to reproduce uncontrollably *[5]*.

It is possible to determine the "erbB2 status" of a tumor, which can be used to predict efficacy of treatment with trastuzumab. If it is determined that a tumor is overexpressing the erbB2 oncogene and the patient has no significant pre-existing heart disease, then a patient is eligible for treatment with trastuzumab *[6]*.Trastuzumab is a monoclonal antibody that interferes with the HER2/neureceptor. Its main use is to treat certain breast cancers.HER2 extends across the cell membrane, and carries signals from outside the cell to the inside. Signaling compounds called mitogens (specifically EGF in this case) arrive at the cell membrane, and bind to the extracellular domain of the HER family of receptors. Those bound proteins then link (dimerize), activating the receptor. HER2 sends a signal from its intracellular domain, activating several different biochemical pathways. These include the PI3K/Akt pathway and the MAPK pathway. Signals on these pathways promote cell proliferation and the growth of blood vessels to nourish the tumor (angiogenesis) *[7]*.

other sub-types of breast cancer. Some cancers develop from pre-invasive lesions such as ductal carcinoma in situ.

The diagnosis of breast cancer is confirmed by taking a biopsy of the concerning lump. Once the diagnosis is made, further tests are done to determine if the cancer has spread beyond the breast and which treatments it may respond to *[2]*.

The incidence of breast cancer varies greatly around the world: it is lowest in less-developed countries and greatest in the more-developed countries. In the twelve world regions, the annual age-standardized incidence rates per 100,000 women are as follows: in Eastern Asia, 18; South Central Asia, 22; sub-Saharan Africa, 22; South-Eastern Asia, 26; North Africa and Western Asia, 28; South and Central America, 42; Eastern Europe, 49; Southern Europe, 56; Northern Europe, 73; Oceania, 74; Western Europe, 78; and in North America, 90 *[3]*.

Worldwide, breast cancer is the most common invasive cancer in women. It affects women and 16% of all female cancers. In 2012, it comprised 25.2% of cancers diagnosed in women, making it the most common female cancer [4].

The HER receptors are proteins that are embedded in the cell membrane and communicate molecular signals from outside the cell (molecules called EGFs) to inside the

- All patients had received adjuvant chemotherapy and 1 year of TRASTUZUMAB
- No Cardiac comorbidities

2.2. All females were subjected to:

A-At the 1st presentation:

1-History taking including: Age, sex, residence, special habit. 2-Family history, similar condition in the family. 3-past history. 4-Any comorbidity (mainly cardiac conditions). 5-Menstrual history. 6-Time of the first presentation.

7-Presenting symptoms. 8-Time of the start of treatment. 9-We used the documented data in the files of the patients including the pathology of breast cancer(including type & pathology), previous surgery, proper staging, metastatic work up, hormonal status, neoadjuvant, adjuvant chemotherapy, radiotherapy, endocrinal therapy and finally the treatment outcome. 10- Estimation of follow up periods (including DFS, OS).

B-Investigations:

- Echocardiography at the start of treatment for all patients.
- Routinely Echocardiography during the period of trastuzumab therapy.
- Base line routine metastatic work up.
- Hormonal profile status by (IHC).
- (SISH) for equivocal her2.

C. Statistical methodology:

1. Data were statistically described in terms of mean ± standard deviation (± SD), and range,

Trastuzumab binds to domain IV of the extracellular segment of the HER2/neu receptor. Cells treated with trastuzumab undergo arrest during the G1 phase of the cell cycle so there is reduced proliferation. It has been suggested that trastuzumab does not alter HER-2 expression, but downregulates activation of AKT*[8]*.

In addition, trastuzumab suppresses angiogenesis both by induction of antiangiogenic factors and repression of proangiogenic factors. It is thought that a contribution to the unregulated growth observed in cancer could be due to proteolytic cleavage of HER2/neu that results in the release of the extracellular domain. One of the most relevant proteins that trastuzumab activates is the tumor suppressor p27 (kip1), also known as CDKN1B. Trastuzumab activates p27 by simultaneously inhibiting PI3K/Akt, Mirk, hKIS, pathways*[9]*.

2. Patients and Methods

This was a retrospective descriptive study performed in clinical oncology clinic at Beni-Suef University hospital and from the insurance hospital at Beni-Suef city within six months from March to September 2016 involving 50 female patients.

2.1.Inclusion criteria

- Female patients
- Non metastatic breast cancer from the start
- Post operative , all patients underwent breast surgery

and one way ANOVA test. Exact test was used instead when the expected frequency is less than 5.

3. Results

This was a retrospective descriptive study performed in clinical oncology clinic at Beni-Suef University hospital and from the insurance hospital at Beni-Suef city within six months from March to September 2016 involving 50 female patients**,** all patients received adjuvant chemotherapy and 1 year of adjuvant trastuzumab**.** According to treatment outcome, all the included patients in that study didn't have any metastatic disease anywhere from the start of their presentation, but during their follow up and the journey of treatment 4 patients (8%) developed systemic metastasis after the end of adjuvant chemo & radio therapy and adjuvant trastuzumab**.** 40% of the cases (n=20) were ER, PR +ve and 60% (n=30) were ER, PR –ve.

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or frequencies (number of cases) and percentages when appropriate.

2. Comparison between the study groups done by using Chi square (χ^2) test, Student t-test

Table (1): comparison of pathology in the 2 previous mentioned groups of breast cancer patients

	Treatment outcome		**P value**
	Develope metastasis/no=4	**Disease free/no=46**	
Pathology, type (%)			
• Invasive duct carcinoma (IDC)	4(100)	42(91.3)	
• Invasive lobular carcinoma (ILC)	0(0)	4(8.7)	0.539
Pathological stage, no. (%)			
• Ia	0(0)	4(8.7)	
• IIa	0(0)	13(28.3)	
• IIb	1(25)	7(15.2)	0.571
• IIIa	1(25)	12(26.1)	
• IIIc	2(50)	10(21.7)	

p-value › 0.05(Non-significant)

Table (1): show no statistically significant difference between patients who still disease free till the end of the study and patients who developed systemic metastasis as regards pathology (type & stage).

Table (2): comparison of DFS in the 2 previous mentioned groups of breast cancer patients

	Treatment outcome		**P value**
	Develope metastasis (no=4)	**Disease free (no=46)**	
Disease free survival, no. (%)			
• Disease free for only that period	4(100)	0(0)	
then become metastatic	0(0)	18(39.1)	**0.001****
• Hormonal treatment (TAM)	0(0)	28(60.9)	
• Disease free till now			

P-value ‹ 0.05(significant)

Table (2): show statistically significant difference between patients who still disease free till the end of the study and patients who developed systemic metastasis as regards disease free survival.

Table (3): comparison of different types of treatment in the 2 previous mentioned groups of breast cancer patients

	Hormonal status		**P value**
	ER,PR+ve (no=20)	**ER,PR –ve (no=30)**	
Neo adjuvant chemotherapy, no. (%)			
• No	18(90)	26(86.7)	
• Yes (FAC and AC)	2(10)	4(13.3)	0.725
Type of surgery, no. (%)			
• Modified radical mastectomy (MRM)	14(70)	24(80)	0.422
• Breast conservative surgery (BCS)	6(30)	6(20)	
Adjuvant chemotherapy, no. (%)			
• (P)	2(10)	4(13.3)	
• (AC, FAC__P, FEC__P, FEC__D, AC_P, AC_D)	18(90)	26(86.7)	0.725
Adjuvant radiotherapy, no. (%)			
• No	1(5)	10(33.3)	**0.019***
• Yes	19(95)	20(66.7)	

P-value ‹ 0.05(significant), p-value › 0.05(Non-significant)

Table (3): show statistically significant difference between patients who received endocrinal therapy and who didn't receive endocrinal therapy as regards adjuvant radiotherapy and but no significant difference as regards neoadjuvant treatment, type of surgery and adjuvant chemotherapy.

Table (4), figure (1): comparison of DFS in the 2 previous mentioned groups of breast cancer patients

	Hormonal status		P value
	ER,PR+ve (n0=20)	ER,PR-ve (no=30)	
Diseases free survival, no. (%) • No • Develope metastatsis	 20(100) 0(0)	 26(86.7) 4(13.3)	**0.092**
Diseases free survival, no. (%) • Disease free for only some period • endocrinal therapy • Disease free till now	 0(0) 18(90) 26(86.7)	 4(13.3) 0(0) 2(10)	**0.001****

P-value › 0.05(Non-significant)

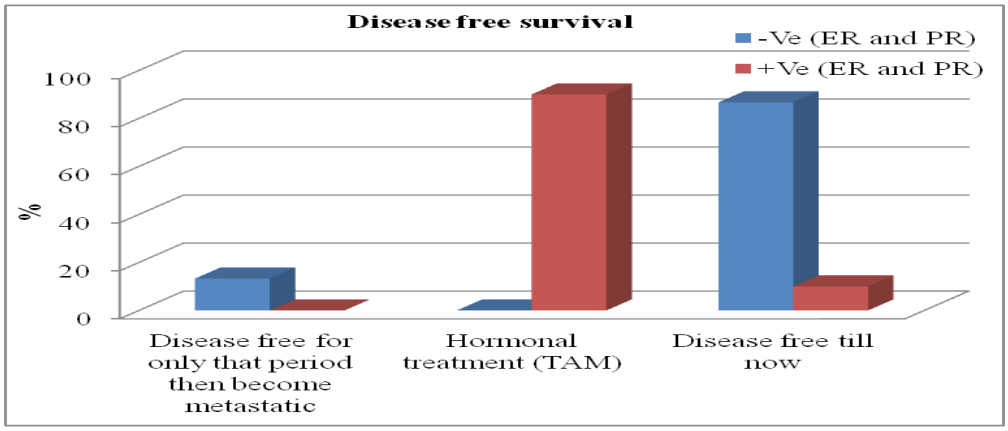
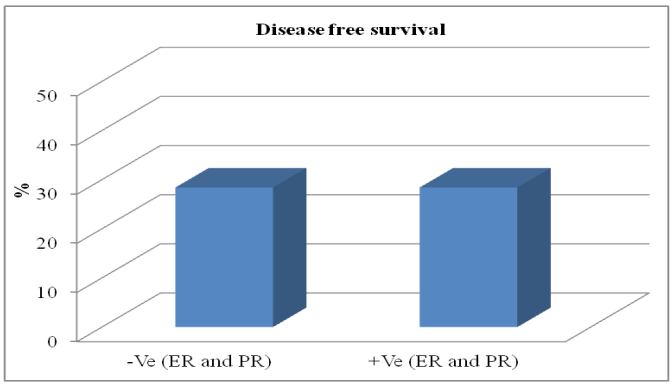


Table (4), figure (1): show was statistically significant difference between patients who received endocrinal therapy and who didn't receive endocrinal therapy as regards disease free survival DFS.

Table (5), figure (2): comparison of OS in 2 previous mentioned groups of breast cancer patients

	Hormonal status		P value
	ER,PR+ve (no=20)	ER,PR –ve (no=30)	
Overall survival (month) Range Mean±SD	 18-42 28.4±5.8	 16-52 28.4±8.2	0.988



P-value › 0.05(Non-significant)

patients in that study were still alive till the end of the study on septemper,2016 and about 8% (n=4) vs 92% (n=46) of patients developed distant metastatsis *(p value= 0.001)* ,that correlated with study [11] in which 2749 female patients with a median follow up of 3.4 years, 467 relapses and 202 deaths were recorded among these patients in the study sample , and the frequency of these events was higher in the "delay" cohort vs the "no delay" cohort :24.3 vs 15.2% patients experienced a relapse, 11.6 vs 6.3% patients died, and 26.8 vs 17.6%patients either had a relapse or died (*p<0.001 for all outcomes).*

In this study, all the 50 recruited patients had received adjuvant chemotherapy & adjuvant 1 year of trastuzumab , 12% of patients (n=6) received neoadjuvant chemotherapy , 78% of patients (n=39) received adjuvant radiotherapy (were node positive) with a significant impact on DFS & OS as demonstrated in many published study [12] shared in the Herceptin Adjuvant (HERA) (Breast International Group [BIG] 01-01) trial. This trail is an international, intergroup, open-label, phase 3 randomized trial published onN Engl J Med, studiedabout 3,399 patients and investigated whether the administration of trastuzumab was effective as adjuvant treatment for HER2-positive breast cancer if used after completion of the primary treatment (e.g., surgery, radiotherapy, and chemotherapy given preoperatively [neoadjuvant], Table (5), figure (2): show no statistically significant difference between patients who received endocrinal therapy patients who didn't receive endocrinal therapy as regards overall survival OS.

4. Discussion

About 10-15% of the newly diagnosed breast cancers have high amounts of a protein called HER2 on the surface of the cancer cells (called HER2 positive breast cancer or HER2 over expression*).*Patients with HER-2–positive disease demonstrate adverse disease characteristics at presentation (larger tumor size, higher tumor grade, and lymph node invasion), have shorter survival times, and have a higher risk for disease recurrence or progression. These features highlight the attractiveness of HER-2 as a potential treatment target ***[10].***

In this study, we presented data on 50 female patients , diagnosed as her2 positive breast cancer, 25 of them (50%) were diagnosed as early stages , the others were diagnosed as advanced stages . About 20 patients (40%) were ER,PR +ve & (60%) were ER,PR –ve, with median follow up 26,66 months. In this study the 50 female patients had received 1 year of adjuvant TRASTUZUMAB without delaying in intiation ≤ 6 months after diagnosis , and that had significant effects on overall survival OS and disease free survival DFS , all the recruited

patients had died during a median follow-up of 65 months.

For both primary and secondary efficacy end points, a significant benefit with respect to disease-free and overall survival was seen in both groups treated with trastuzumab-containing regimens, as compared with the group that received AC-T (standard therapy), which had a 5-year rate of disease-free survival of 75 % and a rate of overall survival of 87% . For patients receiving AC-T plus trastuzumab, the 5-year rate of disease-free survival was 84% (hazard ratio for the comparison with AC-T, 0.64; P<0.001), and the rate of overall survival was 92% (hazard ratio, 0.63; P<0.001). For patients receiving TCH, the 5-year rate of disease-free survival was 81% (hazard ratio, 0.75; P = 0.04), and the rate of overall survival was 91% (hazard ratio, 0.77; P = 0.04).

Also a published a study called NSABP B-31 and NCCTG N9831 at J Clin Oncol [15], about 4,046 patients with HER2-positive operable breast cancer were enrolled to receive doxorubicin and cyclophosphamide followed by paclitaxel with or without trastuzumab in both trials .Median time on study was 8.4 years. Adding trastuzumab to chemotherapy led to a 37% relative improvement in OS (hazard ratio [HR], 0.63; 95% CI, 0.54 to 0.73; *P*< .001) and an increase in 10-year OS rate from 75.2% to 84%. These results were accompanied by an improvement in DFS of postoperatively [adjuvant], or both). The administration of trastuzumab after chemotherapy permits the application of their findings to the wide variety of chemotherapy regimens used throughout the world**.**

The results of HERA trial indicate that one year of adjuvant trastuzumab should be considered a standard on completion of locoregional therapy and neoadjuvant or adjuvant chemotherapy for women who fulfill the study eligibility criteria used in the HERA trial. This study indicated that adding trastuzumab to chemotherapy had improved overall survival by 6% (79% received chemotherapy plus traztuzumab VS 73% received chemotherapy only) [13]**.**

Another study was done by Slamon [14] and Breast cancer International Research Grouphad published at N Engl J Med, randomly assigned 3222 women with HER2-positive early-stage breast cancer to receive doxorubicin and cyclophosphamide followed by docetaxel every 3 weeks (AC-T), the same regimen plus 52 weeks of trastuzumab (AC-T plus trastuzumab), or docetaxel and carboplatin plus 52 weeks of trastuzumab (TCH). The primary study end point was disease-free survival. Secondary end points were overall survival and safety. At the time of this analysis, 656 disease-free survival events were observed (257 in the group receiving AC-T, 185 in the group receiving AC-T plus trastuzumab, and 214 in the group receiving TCH). At this point, 348

This correlated with our analytic study. In our study, among ER, PR positive patients (n=20) of those who received adjuvant trastuzumab & adjuvant endocrinal therapy they didn't develop any distant recurrences. Among EP, PR negative patients (n=30) of those who received adjuvant trastuzumab BUT didn't receive adjuvant endocrinal therapy. In another published data corresponding to the above, working on patients with hormone-receptor-positive disease, the absolute reduction in the rate of distant recurrence as a first event continues to improve over time with the addition of trastuzumab, and reaches 9.6% at 10 years.

For patients with hormone-receptor-negative disease, the absolute risk of distant recurrence as a first event is reduced by 9.6% at 7 years, after which distant recurrence from breast cancer is unlikely that was a presented data from the final planned joint analysis of overall survival from the NSABP B-31 and NCCTG N9831 trials at the 35th Annual San Antonio Breast Cancer Symposium (SABCS) *[19]*.

This study was a retrospective analysis for patients treated in one place and the results cannot be generalized, and this can be explained by the lower patients number and shorter follow up periods, however it may help to highlight the efficacy of TRASTUZUMAB as a standard in the treatment of her2 over expression breast cancer patients and to

40% (HR, 0.60; 95% CI, 0.53 to 0.68; *P*< .001) and increase in 10-year DFS rate from 62.2% to 73.7%. All patient subgroups benefited from addition of this targeted anti-HER2 agent DAHABREH [16] identified five eligible trials , reporting on 13,493 patients with HER-2–positive early breast cancer, 8,627 assigned to chemotherapy combined with trastuzumab and 4,866 assigned to chemotherapy alone , the included trials were HERA , NCCTG N9831 , NSABP B-31 , BCIRG 006 and FinHER with median follow up 2, 2.9, 2.9 ,3 and 3 years respectively .

They performed a systematic review of the published literature and abstracts presented at major oncology meetings to identify the most recent updates of these trials. By combining their results in a metaanalysis, they demonstrated a 38% lower DFS event rate and a similar 34% difference in overall survival favoring the administration of trastuzumab [17]. Notably, the size of these benefits for patients with HER-2–positive tumors, traditionally considered to carry a negative prognosis, is comparable with those conferred by the use of adjuvant tamoxifen for patients with hormone receptor–positive disease, a subtype with a relatively good prognosis. The beneficial effects of trastuzumab in terms of survival were also associated with a significantly lower risk for both locoregional and distant recurrence *[18]*.

emphasis on the value of providing the drug in the developing countries.

5. Conclusion and Recommendations

Receiving TRASTUZUMAB without delaying in intiation (≤ 6 months) after diagnosis offers a dramatic effects on overall survival OS and disease free survival DFS. All newly diagnosed invasive breast cancers should be tested for HER2/neu because HER2-positive cancers are much more likely to benefit from treatment with drugs that target the HER2/neu protein, such as trastuzumab.

References

1. Saunders, Christobel, Jassal and Sunil. Breast cancer (1. ed.). Oxford: Oxford University Press.2009; p. Chapter 1.
2. World Cancer Report. World Health Organization. 2014;pp. Chapter 5.2.
3. Stewart BW and Kleihues P. World Cancer Report. IARC Press. Lyon. 2003Archived 20 October 2008 at the Wayback Machine
4. McGuire A, Brown JA, Malone C, McLaughlin R and Kerin MJ. Effects of age on the detection and management of breast cancer. Cancers, 2015; 7 (2): 908–929.
5. Hudis CA. Trastuzumab--mechanism of action and use in clinical practice. N Engl J Med, 2007; 357 (1): 39–51.
6. Yu D and Hung M. Overexpression of ErbB2 in cancer and ErbB2-targeting strategies. Oncogene, 2000; 19 (53): 6115–6121.
7. Ménard S, Pupa SM, Campiglio M and Tagliabue E. Biologic and therapeutic role of HER2 in cancer. Oncogene, 2003; 22 (42): 6570–6578
8. Kute T, Lack CM, Willingham M, Bishwokama B, Williams H, Barrett K, Mitchell T and Vaughn JP. Development of Herceptin resistance in breast cancer cells. Cytometry, 2004; 57A (2): 86–93.
9. Le XF, Pruefer F and Bast R. HER2-targeting antibodies modulate the cyclin-dependent kinase inhibitor p27Kip1 via multiple signaling pathways. Cell Cycle, 2005; 4 (1): 87–95.
10. Esserman LJ and Joe BN. Clinical features, diagnosis, and staging of newly diagnosed breast cancer, in Up-to-Date (Burstein H, Vora SR, eds.). J Clin Oncol, 2016; 29 (25): 3366-73.
11. Gianni L, Zambetti M and Clark K. "Gene expression profiles in paraffin-embedded core biopsy tissue predict response to chemotherapy in women with locally advanced breast cancer". J. Clin. Oncol, 2005; 23 (29): 7265–77.
12. Goldhirsch A, Wood WC, Gelber RD, Coates AS, Thurlimann B and Senn H-J. ” updated international expert consensus on the primary therapy of early breast cancer “. J Clin Oncol, 2003; 21: 3357-3365.
13. Pietras RJ, Pegram MD, Finn RS, Maneval DA and Slamon DJ. Remission of human breast cancer xenografts on therapy with

humanized monoclonal antibody to HER2 receptor and DNA-reactive drugs. Oncogene, 1998; 17: 2235-2249.

14. Slamon DJ, Clark GM, Wong SG, Levin WJ, Ullrich A, and McGuire WL. "Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene," Science, 1987; 235(4785): 177–182.
15. Perez EA, Romond EH and Suman VJ. Trastuzumab plus adjuvant chemotherapy for human epidermal growth factor receptor 2-positive breast cancer: planned joint analysis of overall survival from NSABP B-31 and NCCTG N9831. J Clin Oncol, 2014; 32: 3744–3752.
16. Dahabreh I, Linardou H, Siannis F, Fountzil G and Murray S. A Systematic Review and Meta-Analysis of Randomized Controlled Trials, 2008.
17. Smith I, Procter M and Gelber RD. 2-year follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. A randomised controlled trial. Lancet, 2007; 369: 29-36.
18. Hortobagyi GN. Trastuzumab in the treatment of breast cancer. N Engl J Med, 2005; 353:1734-1736.
19. Osterweil N. Ten Years Later, Trastuzumab Survival Advantage 2012 March On: multimedia, available from: http://www.medscape.com/viewarticle/775835.