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Original Article

Comparative Evaluation of Biosimilar Trastuzumab with Reference Trastuzumab Activity in HER2-Positive Breast Cancer Patients

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Abstract

One of the breast cancer subtypes, epidermal growth factor receptor 2 (HER2), accounts for 15% of all breast cancers and is characterized by aggressive behavior and a poor prognosis. For patients with HER2-positive breast cancer, trastuzumab, a monoclonal antibody that targets HER2 receptors, is prescribed in addition to chemotherapy to increase their chances of survival. However, the high expense of this treatment makes it impossible for patients in developing nations to easily afford it and undergo this biological therapy. Consequently, trastuzumab biosimilars have been launched as a substitute that offers comparable effectiveness at a reduced price. This study aimed to compare the biological activity and cardiac safety of reference trastuzumab with biosimilar trastuzumab by monitoring serum levels of the tumor biomarker CA15-3 and evaluating N-terminal pro-B-type natriuretic peptide (NT-proBNP) for the adverse cardiac effects of both treatments on HER2-positive breast cancer patients before and after six cycles of biological therapy. This prospective research was performed on 36 females with metastatic and early-stage HER2-positive breast cancer who visited the Oncology Department at Rizgary Hospital, Erbil, Iraq. The patients were within the age range of 30-80 years old. Eighteen individuals received reference trastuzumab, while the remaining 18 received both chemotherapy and biosimilar trastuzumab. Each patient had a data sheet that contained details from hospital-reserved files. In the Herceptin group, there was an insignificant difference in the median of CA15-3, while no significant difference was detected between the means of NT-proBNP before and after treatment. In the biosimilar group, there was a significant reduction in the median CA15-3 as well as a significant increase in the level of NT-proBNP before and after the treatment. Evaluation of the association of trastuzumab-induced cardiotoxicity during breast cancer treatment with different factors indicated that there might be an increased risk of cardiotoxicity after trastuzumab treatment.

Keywords: Biosimilar trastuzumab, Breast cancer, Chemotherapy, Her2-positive breast cancer, Reference trastuzumab

1. Introduction

Breast cancer (BC) is one of the most frequent cancers in females worldwide, accounting for 25% of all cancer occurrences with an estimated 2.26 million cases in 2020 (1). Breast cancer is the most common cancer type among females in the Kurdistan region of Iraq. A poor prognosis and aggressive tumor behavior are associated with malignancies that overexpress the human epidermal growth factor receptor 2 (HER2) in about 15-20% of the tumors of BC patients. Therefore, HER2 targeting strategies were crucial in the management of patients with breast cancer.

A humanized immunoglobulin G1 monoclonal antibody called trastuzumab (TZ) binds to the

extracellular domain IV of HER2 and prevents it from being activated by obstructing different intracellular signaling pathways. It also increases the degradation of HER2 and activates the immune system, which causes cellular toxicity. Both metastatic and early-stage HER2-positive BC are now considered treatable with TZ in combination with chemotherapy. The low effectiveness of adjuvant TZ treatment is offset by favorable efficacy and more significant increases in the survival rates of HER2-positive BC patients when paired with chemotherapy (2).

Due to financial barriers, BC patients in several low-income nations do not have an equal opportunity to acquire TZ. The TZ biosimilars (TBio) can be an option since they are less expensive, offer more accessibility potential, and retain their therapeutic efficacy (3). Drugs that have an active ingredient that is comparable in terms of biological properties, effectiveness, and safety are known as biosimilars.

Biosimilars are now produced by several companies, although there may be discrepancies between biosimilars and the original medication that make doctors less likely to use them, necessitating an assessment of their clinical efficacy and safety profile. Breast cancer cells secrete a protein called Cancer antigen 15-3 (CA15-3), and blood levels of this protein are used to assess the responses of patients to treatment. Compared to baseline readings, CA15-3 reveals BC metastasis and recurrence (4).

Cardiac toxicity is one of the more significant risks of TZ therapy resulting in congestive heart failure, which is still not fully understood. Assessment of N-terminal pro-B-type natriuretic peptide (NT-proBNP) serum level is recommended to monitor heart function and predict adverse cardiac events during TZ adjuvant and neoadjuvant therapy (5). In order to compare the effectiveness of reference TZ and TBio, this study aimed to measure the serum tumor marker CA15-3 and evaluate the levels of the natriuretic peptide NT-proBNP as a predictor of adverse cardiac events.

2. Materials and Methods

This study was performed on 36 female patients with metastatic and early-stage BC within the age range of 30-80 years old, who visited the Oncology Department at Rizgary Hospital, Erbil, Iraq. Eighteen patients received biosimilar TZ, whereas the remaining 18 individuals received reference TZ. Before enrolling in the trial, verbal consent was obtained from each patient.

The physician gave the patients distinct treatment regimes to follow. Eighteen patients received reference TZ, eight patients were instructed to receive Adriamycin-Cyclophosphamide (AC), five patients received Paclitaxel, and five patients received Docetaxel-Carboplatin. Moreover, 10 out of the 18 patients who received biosimilars were instructed to receive Paclitaxel, five patients received AC, and three patients received Docetaxel-Carboplatin. A data sheet was constructed for each patient, including all baseline characteristics, hormonal status, stage of diagnosed breast cancer, type of chemotherapy, and number of received cycles, as well as baseline and follow-up safety profile. Blood samples were taken from each participant before administration of either TZ or the biosimilar. The serum was separated from a blood sample for the assessment of biomarker CA15-3 and NT-proBNP, before and after the administration of six cycles of biological therapy.

3. Results

In total, 36 patients were included in the study with a mean age of 48.1±10.7 years old, a median age of 48.5 years old, and an age range of 32-81 years old. Half of the patients received Herceptin, and the other half received biosimilar treatment.

According to table 1, the most significant proportion (36.1%) of the sample was 40-49 years old; however, there were insignificant differences between the two groups in terms of the age distribution (P=0.655) and

the means and mean ranks of age (*P*=0.481). More than half (61.1%) of the subjects were obese (66.7% and 55.6% of the Herceptin and biosimilar groups, respectively); however, the difference between the groups was not significant (*P*=0.891). Around half (41.7%) of the patients received Taxol, 36.1% received Adriamycin and cyclophosphamide, and 22.2% received Taxotere and carboplatin; however, the difference between the groups was not significant (*P*=0.282) as summarized in table 1 and figures 1-3.

Table 1. Basic characteristics

	Herceptin	Biosimilar	Total	
	No. (%)	No. (%)	No. (%)	p
Age				
30-39	6 (33.3)	3 (16.7)	9 (25.0)	
40-49	5 (27.8)	8 (44.4)	13 (36.1)	
50-59	5 (27.8)	5 (27.8)	10 (27.8)	
≥ 60	2 (11.1)	2 (11.1)	4 (11.1)	0.655*
Mean (SD)	46.8 (11.2)	49.3 (10.4)	48.1 (10.7)	0.481**
BMI				
< 25	3 (16.7)	3 (16.7)	6 (16.7)	
25-29	3 (16.7)	5 (27.8)	8 (22.2)	
≥ 30	12 (66.7)	10 (55.6)	22 (61.1)	0.891*
Type of chemotherapy				
Adriamycin and cyclophosphamide	8 (44.4)	5 (27.8)	13 (36.1)	
Taxol	5 (27.8)	10 (55.6)	15 (41.7)	
Taxotere and carboplatin	5 (27.8)	3 (16.7)	8 (22.2)	0.282*
Total	18 (100.0)	18 (100.0)	36 (100.0)	

*By Fisher's exact test. **By Mann-Whitney test

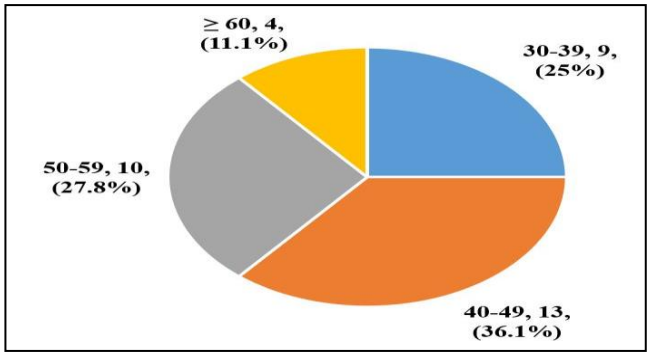

Figure 1. Distribution of sample by age

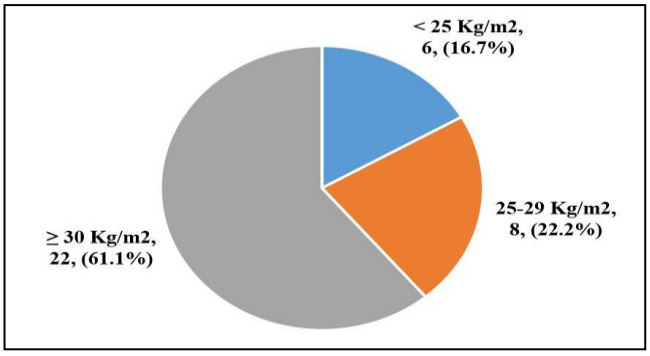

Figure 2. Distribution of sample by BMI

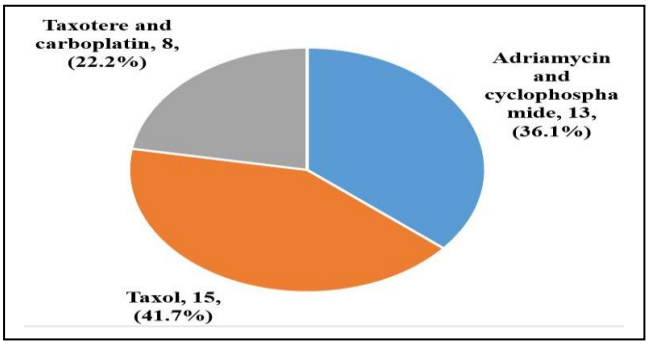

Figure 3. Distribution of sample by type of chemotherapy

In the Herceptin group, there was a decrease in the median of CA15-3; however, this difference was insignificant (*P*=0.526). There were insignificant differences between the mean values of BNP before and after treatment (*P*=0.893) as tabulated in table 2. In the biosimilar group, there was also a significant decrease in the median of CA15-3 from 28.75 before treatment to 19.5 after treatment (*P*=0.018). Moreover, the mean value increased significantly for BNP from 303 before the treatment to 338.67 after the treatment (*P*=0.047).

The differences in the readings of the biomarkers were calculated, either by subtracting the readings before treatment from those after treatment or the reverse (depending on the fact that which value was higher than the other). It is evident in table 3 that all the differences between the two study groups in terms of the mean ranks of the mentioned differences in biomarkers were not significant as follows: CA15 (*P*=0.091) and BNP (*P*=0.279), indicating that both medications had, more or less, the same effect on the biomarkers.

Table 2. Means and medians of biomarkers before and after treatment among patients on Herceptin and patients on biosimilar

	Before			After			
	Mean	**(SD)**	**Median**	**Mean**	**(SD)**	**Median**	**p**
Herceptin							
CA15-3	23.22	(10.19)	23.75	28.24	(20.75)	21.50	0.526*
NT proBNP	284.06	(101.67)	316.00	287.28	(101.59)	301.00	0.893†
Biosimilar							
CA15-3	50.41	(88.89)	28.75	27.68	(32.95)	19.50	0.018*
NT proBNP	303.00	(112.08)	346.50	338.67	(126.21)	369.00	0.047*

†By paired t-test *By Wilcoxon signed rank test

Table 3. Comparing the means and mean ranks of the *difference* between the biomarker's levels before and after treatment of the two treatment groups

	Herceptin			Biosimilar			
Difference	**Mean**	**(SD)**	**Mean rank**	**Mean**	**(SD)**	**Mean rank**	**P***
CA15-3 before - after	-5.02	(24.97)	15.53	22.73	(93.53)	21.47	0.091
NT proBNP after - before	3.22	(100.34)	16.56	35.67	(94.53)	20.44	0.279

*By Mann-Whitney test

4. Discussion

4.1. Age

Females over 50 accounted for around 78% of the new BC cases and usage of 87% of breast cancer-related fatalities in the United States in 2011, demonstrating the importance of age as a risk factor for BC (6). However, the prevalence of BC in younger women has grown globally (7). Breast cancer is the most often diagnosed type of cancer in females over the age of 40 (8).

According to previous studies, younger BC patients had more severe illnesses than older people. After controlling for confounders, middle-aged patients demonstrated a breast cancer-specific survival rate equivalent to young patients but dramatically outperformed young and elderly patients regarding overall survival and breast cancer-specific survival rates. A stratified study revealed that middle-aged patients had a more remarkable survival rate than young patients, with the exception of those with stage III disease. However, age 60 or older was a substantial

independent indicator of a poor outcome (9). Additionally, previous research has found that HER2-positive illness was more prevalent in young individuals (10).

However, the patients in the current research were within the age range of 30-80 years old, which suggests that they were diagnosed with BC while they were young, middle-aged, and older. In the current study, 11.1%, 25%, 36.1%, and 27.8% of the patients were above 60, 30-39, 40-49, and 50-59 years old, respectively, while the remaining subjects were between the ages of 50 and 59.

4.2. Body Mass Index

A higher body mass index (BMI) is linked to a higher chance of acquiring a variety of cancers, including BC that is HER2 positive (11, 12). Indeed, in the present study, the majority of the enrolled patients (61.1%) were obese and had a BMI greater than 30 (66.7% and 55.6% among the Herceptin group and biosimilar groups, respectively). However, no significant differences (P=0.891) were found between the mean BMIs of both groups. A high BMI (>30) is a risk factor for the development of BC due to various factors, such as chronic inflammation linked to high BMI and excessive obesity, higher levels of circulating sex hormones, and high serum leptin. Recent research has shown that a high BMI predicts poor outcomes in those with early BC (13).

Obesity can independently and adversely impact the response rate to neoadjuvant settings, including the complete pathological response, according to an evaluation of the link between obesity and responsiveness to anti-HER2 drugs (14). The CA15-3 is the most prevalent tumor marker utilized for predicting prognosis, monitoring recurrence, and monitoring treatment effects in breast cancer. Circulating tumor markers, such as CA15-3, have been explored as prognostic variables in BC (15).

In the present study, the non-significant (P=0.526) change in serum levels of CA15.3 after administration of TZ may reflect that the patient may not receive a quite effective clinical response to TZ and neoadjuvant therapy. The blood tumor levels of CA15.3 are a topic of debate and discussion despite the fact that monitoring CA15-3 has been utilized as an indicator for the clinical evaluation of the effectiveness of BC treatment (16). Therefore, it cannot be said that those patients did benefit from TZ therapy, depending on this biomarker.

It has been demonstrated in several studies that individuals with BC who had greater blood levels of CA15.3 at the time of diagnosis also had more extensive tumors, axillary node metastases, and more advanced disease stages. According to the results of another previous study, people with BC who have high CA15.3 levels also had a worse prognosis than those who have these markers at normal levels (3).

Even though they do not recommend the usage of CA15.3 alone for the assessment of the response of BC to treatment, the American Society of Clinical Oncology (ASCO) recommendations allow these biomarkers to be used as supplemental evaluations for the selection of treatment for metastatic breast cancer. The ASCO advises that CA15.3 levels be thoroughly watched for the first 4-6 weeks after starting a new medicine since misleading increases may occur (17).

Early measurement of CA15.3 levels in serum for patients with metastatic BC receiving TZ and Paclitaxel can offer insight into the ultimate course of their disease. Accordingly, only a small proportion of patients experience progressive disease among those with a significant drop in biomarker levels (>10%) within the first month of treatment. As a result, continuous serial CA15.3 evaluations during treatment may help monitor the efficacy of HER2-targeted medications and predict the course of illness (18).

In the current study, the median of CA15-3 was decreased. However, the difference was insignificant (P=0.526) in those patients who received reference TZ. In contrast, in the patients who received biosimilar, there was a significant decrease of the median CA15-3 from 28.75 before treatment to 19.5 after treatment

(*P*=0.018). Since patients using anti-HER2 medicine may be at risk of heart damage, cardiovascular monitoring is crucial both before and after the treatment. The National Comprehensive Cancer Network, the European Society of Cardiology, and the European Society of Medical Oncology all advise cardiac imaging evaluations of heart function at 3-month intervals while undergoing treatment (four cycles) (19).

Patients with HER2-positive BC had higher blood levels of NT-proBNP throughout the first year of TZ therapy. Patients with cardiotoxicity displayed a more pronounced rise and had average NT-proBNP levels, more significant than those whose left ventricular function was still intact (20).

The NT-proBNP increases during TZ treatment (21); this rise in NT-proBNP following anthracycline use indicates a 3-12 month timeframe for the onset of cardiotoxicity (22). In the current study, the non-significant difference (*P*-value) among the mean serum levels of NT-proBNP following reference TZ therapy indicated that up to six cycles of treatment with reference TZ had no considerable cardiac adverse effects. While the patients who received biosimilar TZ showed significant differences (*P*-value), the elevation of mean NT-proBNP serum levels predicted a risk factor for the development of cardiac dysfunction or heart failure after six cycles, necessitating further careful evaluation of those patients, discontinuation of biosimilar TZ or switching to a different protocol, and prescription of cardio-protective medication.

However, the results of the present study concerning the non-significant elevation of NT-proBNP levels in the serum of patients on TZ therapy are not in line with those of other studies. Based on previous studies, patients developing TZ-induced cardiotoxicity underwent an increase in NT-proBNP from 198.8±64.0 pg/ml to 678.7±132.4 pg/ml ($P<0.05$) (23).

In the current study, the non-significantly difference (*P*-value) shown in the mean serum levels of NT-proBNP following reference TZ therapy means that up to six cycles of treatment with reference TZ had no considerable cardiac adverse effects. Furthermore, the patients on biosimilar TZ showed significant elevation (*P*-value) of mean NT-proBNP serum levels after six cycles which indicates the prediction of a risk factor for the development of cardiac dysfunction or heart failure. Moreover, it indicates that these patients require further careful evaluation and discontinuation of biosimilar TZ, or they may switch to a different protocol and prescription of cardio-protective medication.

When NT-proBNP levels are over the upper limit of the adjusted normal range, there may be an increased risk of cardiotoxicity following TZ treatment, according to our evaluation of the relationship between TZ-induced cardiotoxicity and several variables. Measurements of NT-proBNP plasma levels can be useful in the determination of the likelihood of cardiotoxicity in BC patients who use TZ.

Authors' Contribution

Study concept and design: V. A. S.
Acquisition of data: N. A. K. M.
Analysis and interpretation of data: N. A. K. M.
Drafting of the manuscript: V. A. S.
Critical revision of the manuscript for important intellectual content: V. A. S.
Statistical analysis: N. A. K. M.
Administrative, technical, and material support: N. A. K. M.

Ethics

Moreover, ethical approval was obtained from the Ethics Committee of the College of Medicine at Hawler Medical University, Erbil, Iraq.

Conflict of Interest

The authors declare that they have no conflict of interest.

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