

Clinical Profile of Carcinoma Breast Patients Treated with Trastuzumab: A Single Centre Study

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How to cite this paper: Jayappa, S.B., Lalkota, B.P., Mani, V., Jenny, R.E., Krishnamurthi, K.P., Sarathy, V., Thineshwaran, S., Nithin, B., Martinovic, S., Ram, A., Patil, S. and Naik, R. (2020) Clinical Profile of Carcinoma Breast Patients Treated with Trastuzumab: A Single Centre Study. *Advances in Breast Cancer Research*, 9, 110-118.

<https://doi.org/10.4236/abcr.2020.94009>

Received: July 10, 2020

Accepted: September 12, 2020

Published: September 15, 2020

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Abstract

Introduction: Breast cancer is the most common female cancer in India and accounting for almost 1 in 4 cancer cases in women worldwide. According to GLOBOCAN 2018: breast cancer incidence is increased to 162,468 in 2018 compared to 144,937 in 2012. Biosimilar drugs allow expanding access to the therapies in the form of cost savings and leading to better overall health outcomes. Our study evaluates the efficacy and safety of Trastuzumab biosimilars and assesses overall survival in the study population. **Materials & Methods:** This prospective study was conducted in Healthcare Global Enterprises Ltd., Bengaluru, India, and all female patients diagnosed with Her2 positive, metastatic (mBC) and Locally advanced breast cancer (LABC), between March 2013 and November 2014, with at least 4 years of post-treatment follow up. **Results:** A total of 65 patients diagnosed with Her2 positive breast cancer and satisfied the selection criteria were included for the study. Partial Response (PR) was observed in 42 (64.6%) patients, Stable Disease (SD) in 11 (16.9%) patients and Progressive Disease (PD) in 12 (18.5%) patients. The overall response rates were 46.1% PR, 30% SD, 23.8% PD in metastatic population and 76% PR, 7.2% SD, 15% PD observed in locally advanced disease. The mean overall survival of the study population was 20.75 ± 15.20 months in metastatic and 29.2 ± 17.06 months in locally advanced patients. **Conclusion:** This prospective study shows the effectiveness of Trastuzumab for HER2-positive in locally advanced and metastatic breast cancer. The response rates, survival and toxicity correlate with other global studies. The response and survival are as same as either generic or original Trastuzumab.

Keywords

Breast Cancer, Trastuzumab, Biosimilars

1. Introduction

Breast cancer is the most common female cancer in India and accounting for almost 1 in 4 cancer cases in women worldwide. According to GLOBOCAN 2018: breast cancer incidence is increased to 162,468 in 2018 compared to 144,937 in 2012 [1]. HER2/neu overexpressed in 20% - 25% of breast cancer patients in Indian population and worldwide [2]. HER2 overexpression is associated with an aggressive clinical phenotype that includes high-grade tumors, increased growth rates, early systemic metastasis, and decreased rates of disease-free and overall survival [3]. Addition of anti-HER2 therapy to chemotherapy, as compared with chemotherapy alone, significantly improves progression-free and overall survival among patients with HER2+ metastatic breast cancer [4]. Trastuzumab is a humanized monoclonal antibody directed to the external domain of HER2 and exerts its antitumor effects by blocking HER2 cleavage, stimulating antibody-dependent, cell-mediated cytotoxicity and inhibiting ligand-independent, HER2-mediated mitogenic signalling [5]. Initially approved by all major regulatory bodies for the treatment of HER2+ metastatic breast cancer (MBC), approved use of Trastuzumab was expanded to HER2+ early breast cancer (EBC) in 2006 [6]. Trastuzumab for 1 year (once in 21 days - 17 cycles) administered with an acceptable chemotherapy regimen is the recommended standard of care according to the guidelines [7] [8]. Clinical trials in HER2+ EBC and MBC have established that treatment with Trastuzumab/chemotherapy increases disease-free and overall survival (OS) [4] [9]. As a result, Trastuzumab has become standard of care in the treatment for Her2+ breast cancer patients. A significant side effect with this drug was cardiac dysfunction, including congestive heart failure (1% - 3%), especially when Trastuzumab was used in combination with anthracycline-based regimens [10]. Trastuzumab related decreased Left Ventricular Ejection Fraction (LVEF) usually resolves after drug discontinuation [11]. Biosimilars are biologic medicines which are highly similar to the reference biological molecule and they demonstrated no differences in the efficacy, safety and purity [12]. Cost savings from the use of a biosimilar might allow for expanded access to the therapies, indirectly leading to better overall health outcomes. Multiple Trastuzumab biosimilars are available in the market. Our study evaluates the efficacy and safety of Trastuzumab biosimilars and assesses overall survival in the study population.

The Objectives of the study:

- 1) To assess the response rate to Trastuzumab therapy in metastatic and non-metastatic breast cancer patients.
- 2) To evaluate overall survival and toxicity in these patients.

2. Materials & Methods

This prospective study was conducted in Healthcare Global Enterprises Ltd., Bengaluru, India. The study included patients who were 20 - 70 years of age and all female patients having histologically or cytologically diagnosed as metastatic or non-metastatic breast cancer, between March 2013 and November 2014, with at least 4 years of follow up post treatment were included in the study. Estrogen Receptor (ER), Progesterone Receptor (PR), Human Epidermal Receptor (HER2), Ki-67% expression, performed by immunohistochemistry (IHC) was obtained from patient case files. When Her2 status was 2+ by IHC, Fluorescence In-Situ Hybridization (FISH) was done to ascertain positivity. Patients who were not willing to undergo treatment with Trastuzumab and who failed to receive minimum 3 cycles of Trastuzumab or defaulted or expired during the course of treatment were excluded from the study. Hormonal Receptor status and Her2 positivity were confirmed prior to initiating chemotherapy. Also, only patients who followed standard guidelines for Trastuzumab (Herclone/Biceltis and Can-mab) were included. Patients received the first dose of Trastuzumab at 8 mg/kg and subsequently, every 21 days received a dose of 6 mg/kg for 17 cycles. All the patients underwent CT/MRI/PETCT scan before and after treatment with Trastuzumab were assessed response (Partial Response—PR, Stable Disease—SD and Progressive Disease—PD). Electrocardiogram (ECG) and echocardiogram (ECHO) to assess cardiac toxicity [Left Ventricular Ejection Fraction—LVEF] before starting therapy and 3 - 6 cycles after therapy. Toxicity was considered, when LVEF drop by >10% after treatment with Trastuzumab. All these clinical information extracted from patient case files.

Statistical Analysis:

Data was analysed using SPSS 10.0 software (Inc., Chicago, III., USA), and descriptive statistics were used to determine the patient's clinical characteristics. The chi-square test was used to compare categorical tumor features in the HER2 positive breast cancer patients. Overall Survival (OS) was the time from initial diagnosis of breast cancer to death/lost to follow-up. Kaplan Meier and log rank tests were used for the analysis of OS. For all the analyses, a α of ≤ 0.05 was considered statistically significant.

3. Results

A total of 65 patients diagnosed with Her2 positive breast cancer and satisfied the selection criteria were included for the study. Amongst the sample, 26 (40%) patients presented with metastatic disease and 39 (60%) were locally advanced. The age of patients in the study was 53.23 ± 10.79 years. Patient's with PS0 (n = 1, 1.5%), PS1 (n = 46, 70.8%), PS2 (n = 18, 27.8%). Forty-four (68.8%) patients were post-menopausal. Hormonal positivity was observed in n = 31 (47.7%) patients, hormonal negative in 34 (52.3%). Ki-67% expression levels were available for 65 patients and 64 (98.4%) patients had Ki-67 > 20%. HER2 by IHC 3+ expressed in 45 (69.2%) patients and IHC 2+ were confirmed by FISH were 20

(30.8%) patients (Table 1).

Response was evaluated in all 65 patients who were treated with Trastuzumab. The overall response of study population in mBC was 46.1% PR, 30% SD, 23.8% PD and in Locally advanced it was 76% PR, 7.2% SD, 15% PD (Table 2). In ER, PR-Her2 positive patients, the response rates in mBC were Partial Response (PR) 47%, Stable Disease (SD) 35%, Progressive Disease (PD) 17.8% and in locally advanced, 76.4% PR, SD, 11.7% PD. Similarly, in triple positive patients, response rates in mBC were 44.4% PR, 22.2% SD, 33.3% PD and in locally advanced, 77.2% PR, 4.5% SD, 18.1% PD. The response rates with Herclone/Biceltis were 55.5% PR, 25% SD, 20% PD in metastatic and 87.5% PR, 8.3% SD, 4.1% PD in locally advanced patients. Biosimilar Canmab has shown 16.6% PR, 50%

Table 1. Baseline patient clinical characteristics of study sample.

Characteristics	Overall	Metastatic	Locally Advanced
Median Age	53.00 ± 10.787	50.62 ± 10.02	54.97 ± 11.06
Chemo duration	3 weekly	3 weekly	3 weekly
Pre-menopausal	20/65	11/26	9/39
Post-menopausal	45/65	15/26	30/39
HER2 by IHC 3+	45/65	17/26	28/39
HER2 (IHC 2+) confirmed by FISH	20/65	9/26	11/39
Hormonal status (ER, PR, HER2 neu)			
Triple Positive	31/65	9/26	22/39
ER & PR negative, HER2 positive	34/65	17/26	17/39
Chemotherapy regimen			
AC → Paclitaxel + Trastuzumab	30/65	15/26	25/39
TCH	35/65	13/26	22/39
Ki 67 > 20	64/65	26/26	38/39
Ki 67 < 20	1/65	1/26	0/39

Table 2. Response Rates of patient characteristics.

Subgroups		Metastatic			Locally Advanced			p-value (Mantel Cox Log Rank Test)
		PR	SD	PD	PR	SD	PD	
Hormonal Subtypes	ERPR-Her2+	8/17 (47%)	6/17 (35%)	3/17 (17.8%)	13/17 (76.4%)	2/17 (11.7%)	2/17 (11.7%)	0.190
	Triple Positive	4/9 (44.4%)	2/9 (22.2%)	3/9 (33.3%)	17/22 (77.2%)	1/22 (4.5%)	4/22 (18.1%)	
Trastuzumab	Herclone/Biceltis	11/20 (55%)	5/20 (25%)	4/20 (20%)	21/24 (87.5%)	2/24 (8.3%)	1/24 (4.1%)	0.520
	Canmab	1/6 (16.6%)	3/6 (50%)	2/6 (33.3%)	9/15 (60%)	1/15 (6.6%)	5/15 (33.3%)	
Overall	response	12/26 (46.1%)	8/26 (30%)	6/26 (23.8%)	30/39 (76%)	3/39 (7.2%)	6/39 (15%)	0.368

SD, 33.3% PD in metastatic and 60% PR, 6.6% SD, 33.3% PD in locally advanced patients.

Locally advanced patients shown better overall response (72% vs 47.6%) and less progressive disease (15% vs 23.8%) when compared to metastatic patients. The mean overall survival of the study population was 20.75 ± 15.20 months in metastatic and 29.2 ± 17.06 months in locally advanced patients. The main toxicity of Trastuzumab, cardiotoxicity (EF drop) was observed <10% in 54 (83.1%) and in 11 (16.9%) patients (**Table 3**). The p-value was not significant, as the study population number was small.

4. Discussion

The frequency of breast cancer has increased rapidly over the last decades especially in premenopausal women [13]. Breast cancer in India is known to be characterized by a higher prevalence of aggressive breast cancers with lower rates of estrogen and progesterone receptor expression [14] [15]. In a retrospective study by Ghosh *et al.*, estrogen receptor and progesterone receptor were expressed in 56.3% and 53.1% of cases, respectively [16]. In another study by Kaul *et al.*, estrogen and progesterone receptor positivity was noted in 34.5% and 36.4% cases, respectively [17]. Findings of the current study are in agreement with this data. It is well known that patients Trastuzumab concurrent with endocrine therapy more effective than HER2 therapy alone [18]. The addition of other anti-HER2 drugs to Trastuzumab improved median survival and overall survival [19]. In this study, patients were not treated with dual anti-HER2 therapies because of unavailability of the drugs.

The association of hormonal receptor status with the expression of Ki-67 is a relatively active topic of research. While Madani *et al.* note that patients with triple negative breast cancer may have higher Ki-67 as compared to other subtypes [20]. All the patients included in the current study were HER2 positive and almost all of them (64 patients) had Ki-67 values > 20. While this may indicate that the high expression of Ki-67 in Indian patients with breast cancer may be independent of hormonal receptor status. Bustreo *et al.* note that a 20% Ki-67 cut-off may be better than the 14% cut-off for better risk-stratification [21].

Although far from established, Ki-67 expression is known to predict pathological complete response (pCR) rates in patients with breast cancer. Patil *et al.* in their study noted no significant difference between clinical or pathological responders and non-responders with respect to pre-treatment or post-treatment median Ki-67 index [22]. Buzatto *et al.* note that addition of Trastuzumab to neoadjuvant chemotherapy significantly improves pCR rate from 4.8% to 46.8%, regardless of the number of preoperative Trastuzumab cycles [23]. Furthermore,

Table 3. Toxicity of the patients who were enrolled in the study.

Toxicity	≤10% Drop	>10% Drop	p-value (Mantel Cox Log Rank Test)
LV Ejection Fraction	54/65 (83%)	11/65 (17%)	0.625

the study noted that hormone receptors and Ki-67 expressions were not predictive of response. About 23.8% patients in the current study achieved a pathological complete response and all of them had Ki-67 > 20% before treatment initiation.

Results of the current study indicate that overall survival did not differ with respect to hormone-receptor status and Ki-67 expressions. Furthermore, overall survival did not differ between patients on ACTH and TCH regimen. This finding is in concordance with the findings of Reeder-Hayes *et al.*, which notes that the 5-year survival outcomes do not differ between patients on ACTH and TCH regimen [24]. This study noted that patients on TCH regimen may be more likely to complete Trastuzumab regimen. However, in Indian settings cost presents a significant barrier to Trastuzumab in HER-2 positive breast cancer patients [15].

Although biosimilar therapies hold a promise of alleviating the cost burden on access to treatment, data on comparative efficacy and safety is relatively scarce. Results of the current study indicate that overall survival did not differ between patients on Herclone/Biceltis, and Canmab. Even, response rates in original and biosimilar Trastuzumab were not statistically significant because the numbers of patients receiving biosimilar Trastuzumab were less.

According to FDA approval on biosimilars, the response of Trastuzumab with biosimilars was not superior to the generic version Apsangikar *et al.* [25], an Indian study supports the statement.

With respect to cardiac safety of Trastuzumab, it may be important to monitor ejection fraction decreases. However, as per the results of the current study overall survival of patients with >10% drop in ejection fraction did not differ from those with <10% drop. No cardiac related mortality is seen in this study. In the median follow-up of 3 years, the incidence of CHF is not increased.

Large cohort studies and clinical trials were established Trastuzumab efficacy; this study explored a single institution experience with small number of patients.

5. Conclusion

This prospective study shows the effectiveness of Trastuzumab for HER2-positive in locally advanced and metastatic breast cancer. The response rates, survival and toxicity correlate with other global studies. The response and survival are as same as either generic or original Trastuzumab.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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