Original Article

Treatment Challenges and Survival Analysis of Human Epidermal Growth Factor Receptor 2-positive Breast Cancer in Real World

Abstract

Context: Advent of trastuzumab has brought tremendous changes in the survival of human epidermal growth factor receptor 2 (Her2)-positive breast cancer patients. Despite the availability of the drug, it is still out of reach for many patients. There is very limited real world data regarding treatment challenges and survival analysis of these patients. **Aims and Objectives:** Primary objective is disease-free survival (DFS) and secondary objective is overall survival (OS) and toxicity profile. **Statistics:** Statistical analysis is done using GraphPad Prism 7.02. **Materials and Methods:** This is a retrospective study of all patients diagnosed with Her2-positive (Her2+) nonmetastatic invasive breast cancer from January 2007 to December 2013. **Results:** In the period of this study, 885 patients are diagnosed with carcinoma breast, of which 212 are Her2/neu positive (23.9%). Of the 212 patients, only 76 (35.8%) patients received trastuzumab along with chemotherapy. Patients receiving trastuzumab with chemotherapy have longer 5-year DFS compared to those receiving chemotherapy alone, 92% and 52.6%, respectively ($P = 0.0001$). Five-year OS is 90.5% and 41.7% in those patients who received chemotherapy with and without trastuzumab, respectively ($P = 0.0001$). Seven patients (9.45%) developed Grade II reversible diastolic dysfunction. Grade II/III peripheral neuropathy due to paclitaxel is the main adverse effect seen in 21 patients. **Conclusion:** In spite of improvement in DFS and OS with trastuzumab, the number of patient receiving targeted therapy is very low due to financial constraints which need to be addressed to bridge the gap in survival of Her2+ patients.

Keywords: *Breast cancer, human epidermal growth factor receptor 2-positive, India, real world*

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Introduction

Human epidermal growth factor receptor 2 (Her2) is a 185-kd glycoprotein with tyrosine kinase activity. Overexpression of Her2 in breast cancer is a key feature of pathobiology of the disease and is associated with poor prognosis.[1-3] Amplification is the primary mechanism of Her2 overexpression.[4] Approximately 20% of all newly diagnosed invasive breast carcinomas are Her2-positive (Her2+). The proportion is higher among tumors with higher grade and in patients with positive nodal status.

Trastuzumab is a humanized monoclonal antibody directed to the external domain of Her2. Four large randomized trials in early breast cancer have shown that treatment with trastuzumab can significantly improve the patient outcome when given alongside and/or subsequent to adjuvant chemotherapy.[5-8] Decrease in recurrence by approximately one-half and mortality by approximately one-third have been demonstrated with the use of trastuzumab. As a result, trastuzumab has become the standard of care for the treatment of Her2+ early breast cancer.

From the available data, the cost of treating Her2+ breast cancer in adjuvant setting in a developed country varies from US$ 70,000 to 80,000/patient while the Gross National Income per capita is <US$ 10,000 in 70% of the countries in the world with more than 75% of the world population. In many of these countries, there is no insurance cover for patients and the cost of therapy is borne by the patient.

While India has access to highly skilled medical professionals and institutes that can provide the state-of-the-art medical care comparable to the best in the world, these are often limited to major cities and are inaccessible to the poor. India is ranked 135 in the world in terms of the human development index, which assesses

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the long-term progress in health and social well-being of a country.[9] Only 1%–2% of the country's gross domestic product (GDP) goes toward health and an estimated 55% of the population in India is poor by the multidimensional poverty index.[10] Approximately 39 million people are falling below poverty line every year.[11] It is estimated that 80% of medical expenses are met by out-of-pocket expenses, which means majority of them cannot afford expensive treatment. The government-run insurance schemes which are in vogue in some states in India do not provide for expensive treatments such as monoclonal antibodies. All these ultimately make the patients' abandon the expensive part of therapy, however, best the outcome might be.

Although significant advances have been made in the adjuvant treatment of Her2+ breast cancer, majority of them are based on well-controlled clinical trials from countries with universal health care. There is very limited real world data of the epidemiology and clinical outcome of Her2+ breast cancer patients.

Our study reflects the actual number of breast cancer patients with Her2 positivity undergoing treatment in our institute and their survival outcome compared to those not taking trastuzumab and treatment challenges.

Materials and Methods

This is a retrospective study of all the patients diagnosed with Her2+ nonmetastatic breast cancer over a 7-year period from January 2007 to December 2013. Patients who completed locoregional therapy (surgery plus radiotherapy where indicated) are evaluated. Eligibility criteria include tumor size ≥1 cm irrespective of nodal status. Confirmation of the hormonal receptor and Her2+ status of tumors is required in all cases before initiating chemotherapy. A result on Her2/neu immunohistochemistry (IHC) (biogenex) of 3+ (>10% stained cells) is required for Her2 positivity. Positive result from fluorescence *in situ* hybridization (FISH) (PathVysion, Vysis; Her2: CEP17 ratio >2.2) for Her2 amplification is required for tumors with IHC 2+ or FISH-positive according to the 2007 ASCO/ACP Her2/neu testing guidelines.

The primary objective is disease-free survival (DFS), defined as the time from date of starting of chemotherapy with or without trastuzumab to the first occurrence of any of the following events: Recurrence of breast cancer at any site; the development of ipsilateral or contralateral breast cancer; second nonbreast malignant disease other than basal cell or squamous cell carcinoma of the skin or carcinoma *in situ* of the cervix; or death from any cause without documentation of a cancer-related event. Secondary objective includes overall survival (OS) and toxicity profile of trastuzumab and various chemotherapy regimens used. OS is defined as the time from date of starting of chemotherapy to death from any cause or lost to follow-up.

The adverse events are graded according to the Common Terminology Criteria for Adverse Events version 4.0.[12]

Statistics

GraphPad Prism software for Windows Version 7.02 (Graphpad Software, La Jolla California USA, www. graphpad.com) was used to plot the Kaplan–Meier curves for DFS and OS (GraphPad Software, La Jolla, California, USA, www. graphpad.com). Log-rank test was used to calculate P values. $P < 0.05$ was considered as statistically significant.

Results

In the 7-year study, 885 patients are diagnosed with carcinoma breast. Of these, 209 are Her2+ by IHC and 71 are Her2/neu equivocal. Receptor status of all patients is shown in Table 1. Of the 71 Her2 equivocal patients, only ten patients got FISH test done, out of which 3 are positive.

The median age is 50 years (range 27–76) in the study. Baseline demographic, clinicopathological, and treatment characteristics of all Her2+ patients are summarized in Table 2.

Of the 212 Her2+ patients, only 76 (35.8%) patients received trastuzumab along with chemotherapy. Of the 76, 54 patients (71.05%) received treatment under insurance scheme, 14 patients (18.4%) under clinical trial, and eight patients (10.5%) are self-paying which is depicted in Figure 1.

Chemotherapy is anthracycline-based in 97% of patients. Twenty-nine percent received taxane, 58% received radiotherapy. In patients who received trastuzumab along with chemotherapy, the 5-year DFS is 92% while it is 52.6% in patients who received chemotherapy alone ($P = 0.0001$) which is depicted in Figure 2. The 5-year DFS according to the receptor status and treatment received is shown in the Figures 3, 4 and Table 3. Five-year OS is 90.5% and 41.7% in those patients who received chemotherapy with and without trastuzumab, respectively ($P = 0.0001$) which is shown in Figure 5.

Of the 76 patients who received trastuzumab, seven patients (9.2%) developed Grade II diastolic dysfunction requiring withholding of trastuzumab. Trastuzumab was

Table 1: Receptor expression in all patients

Subtype	n (%)
Her2 IHC 3+	209 (21.9)
Her2 IHC 2+	71 (7.4)
Triple negative	214 (24.1)
ER and/or PR-positive	460 (48.3)
Her2+ by FISH	3/10

Her2 – Human epidermal growth factor receptor 2;
IHC – Immunohistochemistry; ER – Estrogen receptor;
PR – Progesterone receptor; FISH – Fluorescence *in situ*
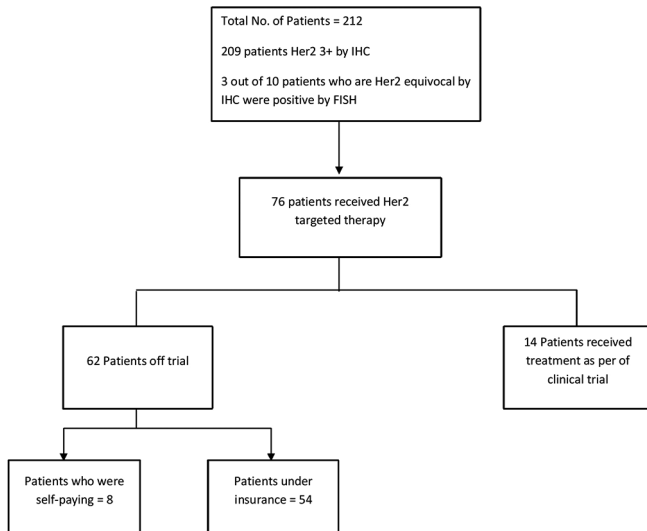hybridization; Her2+ – Her2 positive

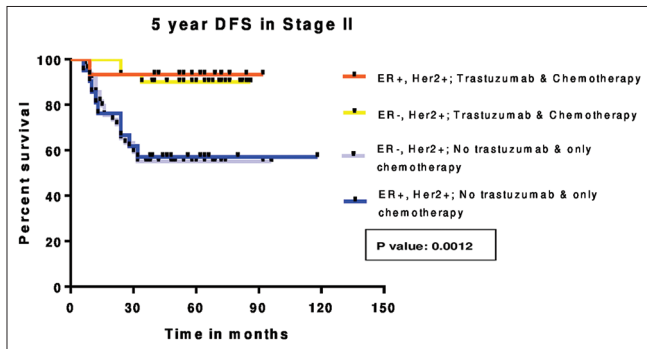Figure 1: Flow chart of treatment schema of all human epidermal growth factor receptor 2-positive patients

Figure 2: Five-year disease-free survival of all human epidermal growth factor receptor 2-positive patients

Figure 3: Five-year disease-free survival in Stage II

Figure 4: Five-year disease-free survival in Stage III

restarted in five patients in 2 months. Grade II/III peripheral neuropathy due to paclitaxel is the main adverse effect seen in 21 patients.

Discussion

The incidence of breast cancer has increased globally over the last several decades;[13-15] with the greatest increase seen in Asian countries such as India, especially in premenopausal women.[16] It is estimated that the incidence has risen by 50% between 1965 and 1985.[17] The rise in incidence of 0.5%–2% per annum has been seen across all regions of India and in all age groups but more so in the younger age groups (<45 years).[18] More than 80% of Indian patients are younger than 60 years of age. With over 120,000 new breast cancer patients being diagnosed annually, it is the most common cancer among women in urban registries where it constitutes >30% of all cancers in female and is the second most common cancer in women after cancer of the uterine cervix in the rural population-based cancer registries of Barshi.[19,20]

The median age of 50 years (range 27–76) in this cohort is strikingly different from that routinely reported in literature
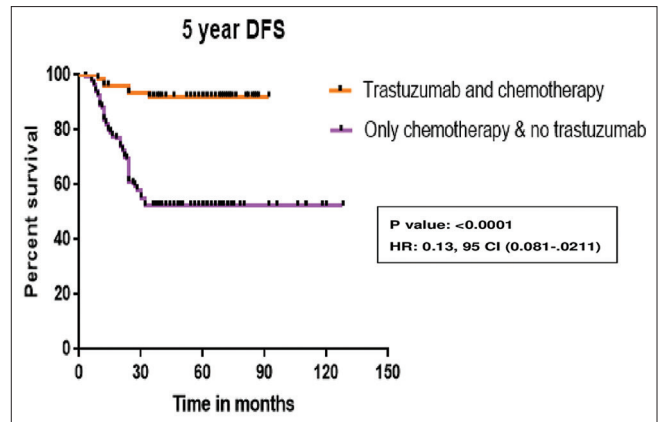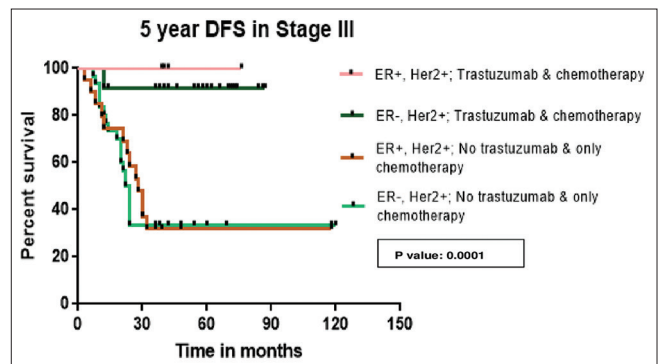
from developed countries where it is 61 years.[21] This lower median age in the present study could be due to a combination tertiary center referral bias and a different population pyramid structure in India and other developing economies, where the proportion of people over the age of 60 years is significantly lower. However, the possible role of additional genetic and environmental factors cannot be excluded.

Advent of trastuzumab has changed the management of breast cancer and the lives of many breast cancer patients worldwide. Although it was approved in adjuvant setting 10 years back, it is not affordable for most of the Indian patients. This single-center retrospective study over a 7-year period illustrates the challenges faced in managing Her2+ breast cancer patients in India. Most of the patients are not able to get the FISH test done if Her2 IHC is equivocal. This reflects challenge at diagnostic level itself.

Of the 212 patients who are diagnosed as positive for Her2, only 76 patients received trastuzumab which reflects the financial situation of the patients. If the patients included in the clinical trial are excluded, the total number of patients are even less.

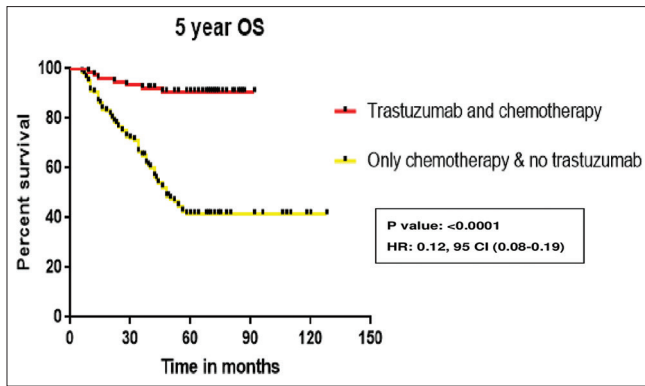Various studies show that the incidence of Her2 positivity in Indian population is between 26% and 50%.[3,22,23] The

Figure 5: Five-year overall survival of all human epidermal growth factor receptor 2-positive patients

Table 2: Baseline demographic, clinicopathological, and treatment characteristics

Characteristics	Number (percentage)
Age (years)	
<60	178 (83.9)
≥60	34 (16.1)
Menopausal status	
Premenopausal	74 (34.9)
Postmenopausal	138 (65.1)
Pathological tumor size	
≤2 cm	31 (14.6)
>2-≤5 cm	123 (58.2)
>5 cm	40 (18.8)
T4	18 (8.4)
Hormone receptor status	
Positive	69 (32.5)
Negative	143 (67.5)
Histological grade	
Well differentiated	108 (50.9)
Moderately differentiated	63 (29.7)
Poorly differentiated	41 (19.3)
Pathological nodal status	
N0	87 (41.0)
N1	74 (34.9)
N2	31 (14.6)
N3	20 (9.4)
Surgery for primary tumor	
Breast-conserving procedure	52 (24.5)
Modified radical mastectomy	160 (75.5)
Radiotherapy	
Yes	122 (57.50)
No	90 (42.5)
Type of adjuvant chemotherapy	
Anthracyclines, no taxanes	68 (32)
Doxorubicin-based regimen	60 (28.3)
Epirubicin-based regimen	8 (3.7)
Anthracyclines and taxanes	68 (32)
Anthracyclines and taxanes with trastuzumab	76 (35.8)
Adjuvant endocrine therapy	
No	143
Yes	69
Tamoxifen	27 (39.1)
Aromatase inhibitors	42 (60.9)

incidence in our study is 23.9%. The exact incidence is yet to be known because a significant proportion of patients with Her2 equivocal are not undergoing further evaluation with FISH due to financial constraints. Significant heterogeneity between different hospitals with regard to diagnostic facilities available and access to trained personnel also contributes to it. In comparison with other studies from India, we found hormone receptor positivity in 41% of patients. This increase is mostly due to the increased and compulsory testing of almost all patients in the past few years.[24,25]

Coleman reported >80% survival from breast cancer in North America and Europe compared with 60% in middle-income countries and 40% in low-income countries.[26] There is a significant difference in the survival rates in developed and developing countries mainly because of a lack of early detection programs and inadequate resources for treatment. A study by Gallagher CM *et al.* showed 5-year OS in patients receiving trastuzumab is 89%, similar to our study.[27] The 5-year OS of 43% in patients treated with chemotherapy alone is similar to other Indian study by Jana *et al.*[28] There are no events relating to relapse after 3 years in our study indicating the aggressiveness and early relapse in patients with Her2+ breast cancer. There is very limited published data with trastuzumab from India, apart from clinical trials regarding the DFS and OS. Our study helps in contributing to literature.

The 9% incidence of cardiotoxicity in our study is similar to the previous studies done by Russell *et al.* and Procter *et al.* and is reversible.[29,30] In five patients, rechallenge with the drug is done without any further complications. No cardiac-related mortality is seen. There is no increase in the incidence of CHF at a median follow-up of 3.3 years.

Different treatment centers in India have different costing structures based on whether they are private for-profit, private nonprofit, and fully or partly government-subsidized hospitals. In spite of these limitations, it is likely that these data are broadly representative of the experience of many

tertiary centers in the country. The cost of treatment is around 1,000,000 ($16,000) with original trastuzumab. With many generics coming into market, the cost may be reduced by 25%. In a country with GDP per capita income of $1581, it is out of reach for most of the patients.[31]

From our data, it is clear to us that the single most important factor for not proceeding with treatment was lack of financial resources (90%) similar to other study from India by Ghosh *et al.*[32] Even though it is in the essential drug list,[33] it is not being provided at free of cost or subsidized price in most of the hospitals. It reiterates the

Table 3: 5-year disease-free survival according to stage

Stage	Trastuzumab and chemotherapy		No trastuzumab and only chemotherapy		*P*
	Number of patients	5-year DFS	Number of patients	5-year DFS	
I					
ER+, Her2+	1	100	6	100	-
ER−, Her2+	1	100	9	100	
II					
ER+, Her2+	15	93.3	21	57.1	0.0012
ER−, Her2+	30	90	49	55.1	
III					
ER+, Her2+	5	100	21	31	0.0001
ER−, Her2+	24	88.4	30	32.1	

DFS – Disease-free survival; ER – Estrogen receptor; Her2 – Human epidermal growth factor receptor 2; Her2+ – Her2-positive

need for incorporation of the drug into national and state health scheme programs. The government must note the importance of drugs which have a major impact on survival, especially in a cancer that is common among population and makes every effort to make it easily accessible.

Conclusion

Although the incidence of Her2 positivity is high, the number of patients actually receiving the targeted therapy is very low. Herculean efforts are need in terms of cost modification to bridge the gap in survival of Her2+ patients.

Financial support and sponsorship

Conflicts of interest

There are no conflicts of interest.

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