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Clinical Outcome and Pattern of Failure in Non Metastatic Her2 Positive Breast Cancer

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ABSTRACT
Breast cancer is the commonest cancer among women, impacting 2.6 million women each year, 24.5% of all cancers in women and also causes the greatest number of cancer-related deaths among women.[1]About 20 - 25% of all invasive breast carcinoma overexpress HER2neu and accounts for increased aggressiveness and decreased disease free survival. With the advent of targeted therapy to HER 2 receptors with or without adjuvant or neoadjuvant chemotherapy has shown to significantly improve survival rates and response rate.

AIM
To assess the loco regional control ,Pattern of failure and effect of duration of Anti-HER2 therapy and overall and disease free survival

MATERIALS AND METHODS
In this Retrospective study design, all patients with non metastatic breast cancer who was HER2 positive who reported to department of Radiation Oncology MCH Kottayam between 1st January 2016 to 31 March 2020 were included. The treatment and follow up details were collected for analysis from the individual patient treatment records.Statistical analyses were done using SPSS software. Any recurrence locally or distant metastasis was noted.Disease Free Survival (DFS) and Overall Survival (OS) were calculated from the date of date of registration to date of disease recurrence or death respectively. The DFS and OS estimations were generated using the Kaplan Meier method and compared using Log Rank tests. The Cox proportional hazards regression model was used for univariate and multivariate analyses of prognostic factors for recurrence and survival.

RESULT:A total of 106 patients were included in the study, all women, majority of whom who belonged to the age group 40 – 60 yrs. 20.8% of the patients had treatment failure causing local recurrence in 3.7%, metastasis in 12.26% and both local recurrence and metastasis in 4.7%. Majority of patients metastasized in visceral organs indicating aggressive nature of tumor biology.A total of 7(6.6%) had features of cardiac toxicity,among whom only one had symptomatic deterioration of ejection fraction.2 year overall survival was 81% and disease free survival was 75 %. The 2 yr disease free survival for patients who received trastuzumab was 76.13% and for those who didn't receive trastuzumab was 54.5%. Among patients who received trastuzumab for 1 year, the 2 year disease free survival 79.6% was comparable to patients who received atleast 6 months(78.1%). There was statistically significant association for stage,perineural invasion and duration of adjuvant targeted therapy with disease free survival.

KEYWORDS: Carcinoma breast, HER2 Positive, Trastuzumab , Duration

I. INTRODUCTION

Carcinoma breast is a heterogenous disease which is the most common cause of cancer related mortality in women in the world[1]There are various subtypes of breast cancer among which HER2 positive breast cancer are known for its aggressive nature and early recurrence.[2] The advent of HER2 targeted therapy has shown to improve the survival rates and reduce recurrences The Human Epidermal Receptor Protein -2 (c-erbB-2 or HER2) oncogene protein is a transmembrane glycoprotein in the epidermal growth factor receptor family[3]. It is expressed at low levels in a variety of normal epithelia, including breast duct epithelium, but amplification of the HER2 gene and concomitant protein overexpression are present in 10-20% of primary breast cancers.This HER-2 oncogene located on chromosome 17q12 encodes for a 185 kD trans membrane glycoprotein receptor (HER2/EGFR2/ErbB2) belonging to the family of tyrosine kinases.

Transmembrane receptors are typically characterized by an extracellular ligand binding domain and intracellular tyrosine kinase domain and a cytoplasmic tail. The tyrosine kinase domains are activated by both homodimerization and

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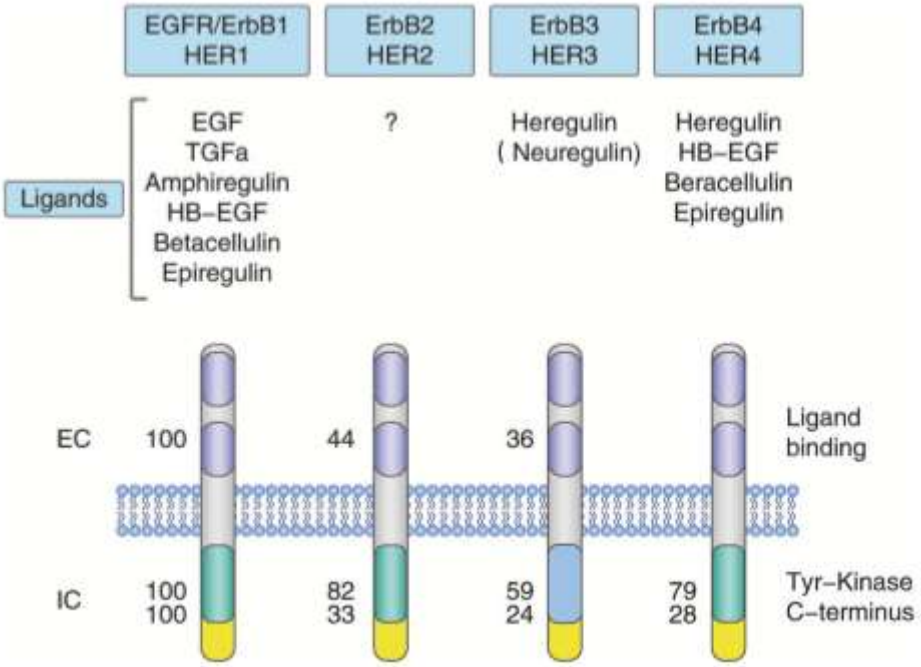
heterodimerization, generally induced by ligand binding. While the other receptors undergo hetero and homo dimerization when ligands attach to their extracellular domain, HER2 has no ligand binding capacity and has a closed configuration, but is the preferred partner during dimerization. Thus, in contrast to the extracellular domains of the three other HER receptors, the extracellular domain of HER2 can adopt a fixed conformation resembling a ligand-activated state, permitting it to dimerize in the absence of a ligand.



TESTING FOR HER2

. It is advised that HER2 testing be carried out using a validated IHC (immune histochemistry) or ISH (in situ hybridization) assay on the invasive component.

IHC staining is reported based on circumferential membrane staining of tumor cells which implies overexpression of the HER2 protein product.[4]

i) If there is complete as well as intense circumferential membrane staining within >10 % of tumor cells, it is considered IHC 3+. All IHC 3+ tumors are considered HER2 positive.

ii) If there is incomplete or weak to moderate circumferential membrane staining within >10 % of tumor cells, or complete and intense circumferential membrane staining within <10 % of tumor cells, it is reported as IHC 2+and are considered HER2 equivocal.

iii) If there is faint or barely demonstrable incomplete membrane staining within >10 % of tumor cells, it is reported as IHC 1+. All IHC 1+ tumors are taken as HER2 negative. if no staining is demonstrated or there is only faint or barely perceptible incomplete membrane staining within <10 % of tumor cells, it is also reported as IHC 0 . These tumors are also reported as HER2 negative.[24]

An equivocal Her2 requires Her2 testing using In Situ Hybridization (ISH) on the same specimen or a new test (using a different specimen with either IHC or ISH).

ISH is the ratio between Her2 and the chromosome 17 enumeration probe (CEP17) which implies the HER2 gene amplification.

ISH positive if the HER2/CEP17 ratio is ≥2.0.This is regardless of the average HER2 copy number signals/cell.

• ISH positivity also includes a HER2/CEP17 ratio <2.0, but the average HER2 copy number is ≥6.0 signals/cell.

• ISH is equivocal if the HER2/CEP17 ratio is <2.0 and the average HER2 copy number is ≥4.0 and <6.0 signals/cell.

• ISH is negative if the HER2/CEP17 ratio is <2.0 and average HER2 copy number is <4.0 signals/cell.

TARGETED THERAPY IN HER2 BREAST CANCER

TRASTUZUMAB

Trastuzumab a monoclonal IgG1 class humanized murine antibody, binding the ECD of HER2 transmembrane receptor. It was first accepted for HER2-targeted breast cancer therapy.[5]

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Its anticancer activity is accomplished by binding to the extracellular domain of the HER2 receptor, which inhibits ligand-independent dimerization of the HER2 receptor as well as antibody-dependent cell-mediated cytotoxicity (ADCC)[6]. Interestingly, the anti-HER2 therapy's mechanism has also been confirmed to involve the prevention of angiogenesis, cell-cycle arrest, and apoptosis, as well as interference with DNA repair and downstream signal transduction pathway blockage[7] Following the phase 3 trial by Slamon and et al., the FDA officially approved the drug in 1998 for the treatment of metastatic breast cancer.[8]
Presently, NCCN Clinical Practice Guidelines recommends the following regimens, for the first-line options of HER2positive metastatic breast carcinoma: trastuzumab plus chemotherapy single agents, either paclitaxel (3 weeks or weekly cycle), docetaxel (3 weeks or weekly cycle), or vinorelbine (weekly).

New anti-HER2 therapies, either as monotherapy or combined with trastuzumab, have demonstrated anti-HER2 tumor activity. Dual distinct anti-HER2 therapies could be combined to achieve synergistic effect. Three combinations are particularly suggestive: (1) Pertuzumab+trastuzumab+docetaxel; (2) Trastuzumab+lapatinib; and (3) Pertuzumab+trastuzumab.

ROLE IN NEOADJUVANT SETTING

HER2-positive breast cancers may have potential chemosensitivity in combination with trastuzumab, in the neoadjuvant treatment[9]

A small randomized trial conducted by the MD Anderson cancer group was perhaps the first study confirming the role of anti-HER2 therapies in the neoadjuvant scenario. Although only 42 cases were enrolled, the competition of trastuzumab to sequential paclitaxel chemotherapy of four cycles followed by FEC of four cycles regimens resulted in an outstanding high rate of 2.5 times (66.7%) of pCR, than chemotherapy-alone arm (25%), p=0.02. Despite the small sample size, the updated versions of this study also confirmed the findings[10]

NOAH trial : a multicenter , open label, randomized trial of 235 patients of which 118 received chemotherapy alone (doxorubicin, paclitaxel, cyclophosphamide, methotrexate and 5 fluoro uracil) and 117 received chemotherapy with 1 year of trastuzumab (concurrently with neoadjuvant chemotherapy and continued as adjuvant therapy). After a median followup of 5.4 yrs, event free survival was 58% in trastuzumab group [EFS in pathological complete response (PFS) was 86%] compared to 43% in chemotherapy alone group.[PCR is 54.8%][11]

NEOSPHERE TRIAL multicentre, open-label, phase 2 study, treatment-naive women with HER2-positive breast cancer were randomly assigned (1:1:1:1) centrally and stratified by operable, locally advanced, and inflammatory breast cancer, and by hormone receptor expression to receive four neoadjuvant cycles of: trastuzumab (8 mg/kg loading dose, followed by 6 mg/kg every 3 weeks) plus docetaxel (75 mg/m(2), escalating, if tolerated, to 100 mg/m(2) every 3 weeks; group A) or pertuzumab (loading dose 840 mg, followed by 420 mg every 3 weeks) and trastuzumab plus docetaxel (group B) or pertuzumab and trastuzumab (group C) or pertuzumab plus docetaxel (group D). The primary endpoint, examined in the intention-to-treat population, was pathological complete response in the breast. **:** Patients given pertuzumab and trastuzumab plus docetaxel (group B) had a significantly improved pathological complete response rate compared with those given trastuzumab plus docetaxel, 29.0% (21–38.5%) in grp A vs 45.8% (36–56%)in group B vs16.8% (10–25%) in group C vs 24.0%(16–34%)in group D without substantial differences in tolerability[12]

In addition, **TECHNO** trial an open label, phase II study demonstrated results of 217 HER2-positive patients with characteristics of larger tumors (≥2cm), who received four cycles of AC (epirubicin and cyclophosphamide, EC), followed by four cycles of TH (paclitaxel and trastuzumab) as neoadjuvant treatment. Overall, pCR was accomplished in nearly 38.7% and 3-year DFS (88% vs 71%; p=0.003) and OS (96% vs 85%; p=0.007) was improved[13]

TRASTUZUMAB IN ADJUVANT SETTING

Large number of studies shows that trastuzumab combined with chemotherapy can reduce nearly 50% RR of recurrence and metastasis

Four significant adjuvant trials have investigated different approaches with trastuzumab as follows: Herceptin® Adjuvant (HERA)[14], North Central Cancer Treatment Group (NCCTG) N9831[15], NSABP B-31[16] and Breast Cancer International Research Group (BCIRG) 006[17] consisting of more than 13,000 female cases with HER2-positive EBC.

PERSEPHONE TRIAL : open label randomized phase 3 non inferiority trial. 2045 patients were treated with 12 month of trastuzumab along with chemotherapy and 2044 patients with 6 months of

trastuzumab with chemotherapy. Median follow up was 5.4 yrs. DFS was 13% in 6 months group and 12% in 1 yr group showing non inferiority of the 6 months treatment along with less cardio toxicity[18]

SOLD trial : Open-label, randomized (1:1) clinical trial including 2168 women with HER2-positive breast cancer. Chemotherapy was identical in the 2 groups, consisting of 3 cycles of 3-weekly docetaxel (either 80 or 100 mg/m2) plus trastuzumab for 9 weeks, followed by 3 cycles of fluorouracil, epirubicin, and cyclophosphamide. Thereafter, no trastuzumab was administered in the 9-week group, whereas controls received trastuzumab to complete 1 year of administration. The median follow-up was 5.2 years. Noninferiority of the 9-week treatment could not be demonstrated for DFS (hazard ratio, 1.39) Distant disease-free survival and overall survival did not differ substantially between the groups. Thirty-six (3%) and 21 (2%) patients in the 1-year and the 9-week groups, respectively, had cardiac failure; the left ventricle ejection fraction was better maintained in the 9-week group[19]

II. RESULT

Out of the patients, 20.8% of the patients had recurred causing local recurrence in 4 (3.7%), metastasis in 13(12.26%)and both local recurrence and metastasis in 5(4.7%). out of the metastasized patients, majority (8.5%) had visceral organ metastasis(lungs,liver) indicating the aggressive nature of the tumor biology.

It was found that Nodal stage had a significant association with local and

distant failure with p value 0.001 with 23% of N1,25% of N2 and 60 % of N3 stage had recurrenceThere were 29% of the study population with Composite stage 1 among whom there was a recurrence rate 6.8%, 30.3% of patients were having stage 2 and 9.6% recurred and among 43.3% with stage 3 , 36% had local or distant recurrence with a significant association with a p value of 0.001 Perineural invasion was found in 9 patients, out of which 5 patients(55%) had local recurrence which are significantly associated with a p value of 0.007.Mc ready et al showed an increase in local recurrence in association with PNI in the tumor.

The duration of adjuvant trastuzumab taken had a significant association with recurrence. Those who did not take adjuvant targeted therapy, 5(45%) recurred. Only 4(7.1%) who received trastuzumab for 1 year had a history of recurrence. And 10(28%)who received trastuzumab for at least 6 months recurred with disease. 2 out of 3 patients who received trastuzumab for less than 6 months recurred locally or with distant metastasis The duration of adjuvant trastuzumab taken had a significant association with recurrence. Those who did not take adjuvant targeted therapy, 5(45%) recurred.

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CARDIAC OUTCOMES

Trastuzumab-induced cardiotoxicity presents with a range of severity from asymptomatic decline in left ventricular ejection fraction (LVEF) to symptomatic heart failure59 and does not appear to be related to either dose or duration .In this study,thecardiotoxicty was found in 7 (6.6%) and only one(0.9%) had symptomatic cardiac dysfunction,which goes in line with findings of Moja et al which described trastuzumab related cardiotoxicity occurred in 5.7–35.4% of patients enrolled in randomized controlled trials. Rates of symptomatic heart failure was 0% to 1.7%

SURVIVAL OUTCOMES

The 2 year disease free survival of the entire cohort was74.8% and overall survival was 81% .

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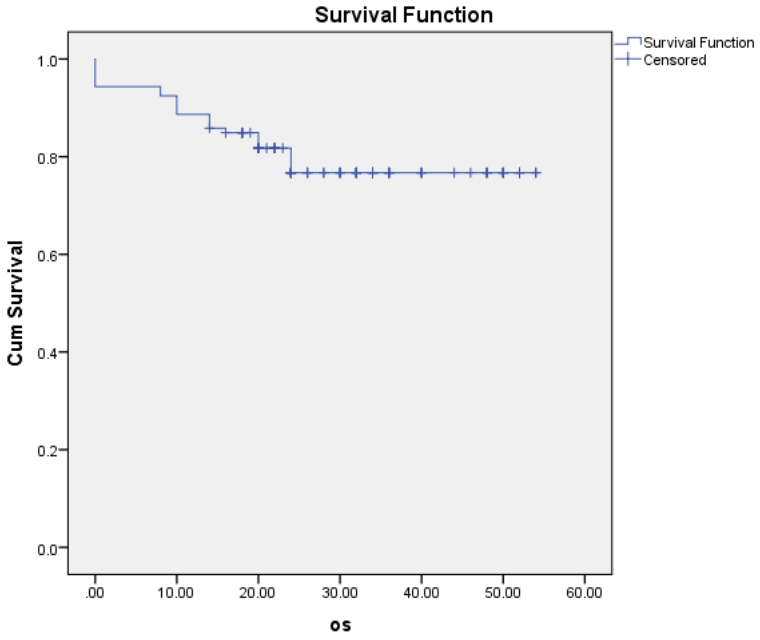
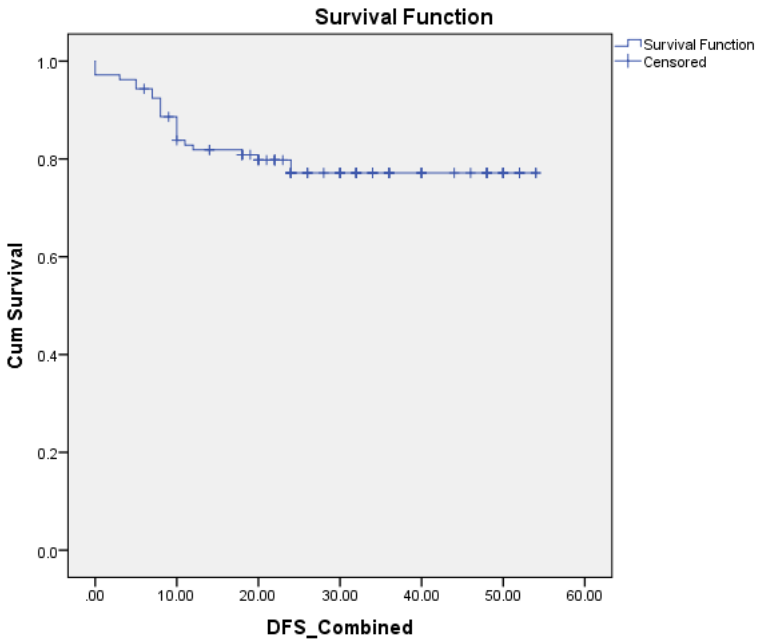


overall survival in months



disease free survival in months

A study by Onitilo et al. which compared the survival and the clinico pathological subtypes in the four breast cancer subtypes had shown an OS and DFS of 84.6% and 75.9% respectively at 5 years for HER2+ breast carcinomas.[20] Another study by ShaheenahDawood et al also demonstrated similar outcomes in HER2positive subtype of breast cancer[21]

There were 48%of patients with T2 disease, among whom 39% had a DFS>2years,15% of T3 disease,of whom 11% had DFS benefit and 29% of T4 disease,among whom only 16% had 2 year DFS. The p value was 0.024 indicating statistically significant association between T stage and DFS.

27.4% of the patients were of composite stage 1, 29.2%in stage 2 and 43.4% in stage 3 breast cancer. On univariate analysis it was found that composite stage has statistically significant association with DFS (p value 0.002) and with overall survival (p

value 0.049) 9%of patients were reported to have PNI, out of whom only 4 (55.5%) had a OS>2 years,which was statistically significant (p value 0.004) and only 3(33.3%) had a DFS > 2 years

Neoadjuvantchemotherapy,majority (76%) anthracycline based followed by taxane based was taken by 43% of the patient, and had a significant association with DFS (p value 0.043)

Response to neoadjuvant chemotherapy with pathological complete response was attained by 15% of patients who took neoadjuvant schedule and has a significant association with OS (p value0.022) and DFS (p value 0.011)

Duration of trastuzumab therapy has a significant association with DFS (p value 0.048).only 50 % of patients who did not take trastuzumab therapy had a DFS >2 years,compared to 79.6% of patients who completed 1 year of trastuzumab had a DFS >2 years, patients who completed atleast 6 months of trastuzumab had 78.1% patients with DFS>2 years,which is comparable. It was in line with the findings of the non inferiority trial of PERSEPHONE without a 3% absolute decrease in DFS to satisfy non inferiority criteria.

III. LIMITATIONS

The main limitations of my study areits retrospective nature,heterogeneity of the treated population,small sample size. ,difficulty in obtaining treatment data from patients not on active follow-up

IV. CONCLUSION

HER2 positivity confers an aggressive nature to breast cancer with a propensity for local recurrence and early metastasis. This study showed the clinical outcome and the recurrence pattern and factors associated with it. It was found that the composite stage, perineural invasion, pathologic response to neoadjuvant chemotherapy and adjuvant HER2 targeted therapy have an association with tumor recurrence and survival rates. Those who took adjuvant targeted therapy had better survival than those who did not take. The survival outcomes of patients with duration of 1 year of targeted therapy and those who completed atleast 6 months were comparable which has an impact on treatment of patients who has financial constraints to complete targeted therapy for 1 year.

DECLARATION BY AUTHORS

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Conflict of interest :The authors declare no conflict of interest

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