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Original Article

Response Assessment to Neoadjuvant Treatment with Dual HER2 Blocker in HER2 positive Early and Locally Advanced Breast Cancer

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ABSTRACT

Objective: To analyze response assessment to dual HER2 blockade in HER2 positive early and advanced breast cancer and to identify factors associated with partial response among the study participants

Study Design: Quasi-experimental study.

Place and Duration of Study: Oncology Department, Combined Military Hospital Rawalpindi, Pakistan, from Sep 2022 to Apr 2023.

Methodology: One hundred and eighty ladies with early and advanced breast cancer who were HER2 neu positive and were given dual HER2 blockade treatment before surgical resection of the tumor. Response was assessed after the surgery on surgical specimen and classed as partial or complete response. Relevant clinical factors were associated with presence of partial response among the women included in the study.

Results: Mean age of the patients was 45.56±9.91 years. Out of 180 patients, 116(32.9%) had complete pathological response while 64(25.6%) had partial response to the neo-adjuvant therapy combined with dual HER2 blockade. Having T1-2N1 disease, ER PR negative and HER2 positive disease, and not having interruptions in treatment due to neutropenia or cardiotoxicity were found associated with complete pathological response to neo-adjuvant medications combined with dual HER2 blockade (p-value<0.05).

Conclusion: Complete pathological response was seen in the majority of patients included in our study. Having T1-2N1 disease, ER PR negative and HER2 positive disease, and not having interruptions in treatment due to neutropenia or cardiotoxicity were factors associated with complete pathological response in our study participants.

Keywords: Breast Cancer, Cancer, HER2 Blockade, Pathological Response.

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INTRODUCTION

Different types of cancers have been notorious to take millions of human lives each year across the globe, including breast cancer.[1] Timely intervention and multidisciplinary approach reduce the mortality and morbidity to large extent.[2] Despite worldwide awareness campaigns, in lower- and middle-income countries, a large number of women present with advanced disease.[3]

Treatment modalities and approaches for patients suffering from breast cancer have been evolving continuously.[4] Patients presenting with advanced disease usually require more aggressive chemotherapeutic regimens in order to reduce mortality and morbidity.[5] Assessing response to treatment is a tricky area and number of criterion have been used but still pathological response on tumor specimen after the surgery is considered gold-standard in clinical practice and further treatment is tailored usually seeing this response.[6]

Dual HER2 neu blockade treatment is in practice for patients presenting with HER2 neu positive early or advanced breast cancer. Studies show that complete pathological response is the best marker to assess the efficacy of any treatment in patients managed for breast cancer and that dual HER2 neu blockade in neo-adjuvant protocol in early HER2 neu positive breast cancer patients were associated with complete response.[7,8] Another study concluded that pathological complete response was better in patients who had dual blockade as compared to patients who were targeted with single agent.[9]

Pakistan is in no way behind in statistics of breast cancer from rest of the world, burdening already strained health resources. A local study compared patients of HER2 positive breast cancer who got neo-adjuvant therapy with and without Trastuzumab.

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They revealed that response was better in patients who took Trastuzumab.[10]

We conducted this study to analyze response assessment to dual HER2 blockade in HER2 positive early and advanced breast cancer and factors associated with partial response.

METHODOLOGY

This Quasi-experimental study was conducted at the Oncology unit of Combined Military Hospital Rawalpindi, Pakistan from September 2022 to April 2023, Ethical approval was obtained from the Institutional Ethical Review Committee (via letter number 380) and other formalities were fulfilled by the team before the commencement of this study.

Inclusion Criteria: Women between the age of 18 and 65 years with early or advance HER2 neu positive breast cancer were included.

Exclusion Criteria: Pregnant patients, those who had already undergone surgery or those who had metastasis at time of presentation, those who were allergic to treatment options used in the study, patients lost to follow-up, and those who stopped treatment against the medical advice were excluded.

Sample size was calculated using WHO calculator taking reported prevalence of complete pathological response in advanced breast cancer as 50%.[10] The estimated sample size came out to be 97. Patients were enrolled using non-probability consecutive sampling, after obtaining written, informed consent.

Patients presenting with early or advanced breast cancer which was HER2 positives were recruited after information from the team regarding study and their rights including right to withdrawal from this study at any given time. All patients underwent detailed clinical and pathological evaluation and diagnosis was done by a classified oncologist of our unit after incorporation of all the relevant findings.[11] Neoadjuvant chemotherapy was given in standard doses as per protocol in our unit based on international guidelines (Anthracyclines, 4 cycles, 3 weekly for 3 months and paclitexal 12 cycles/weekly).[12] Dual HER2 blockade (Herceptin and Perjeta) were given in four doses three weekly for 3 months.[13] Surgery was performed after 4 weeks of chemotherapy. Resected tumor was secured in medium supplied by the laboratory and sent to histopathology department of Armed Forces Institute of Pathology for detailed histopathological assessment. Response on histopathology was classed as partial response and complete response on the basis of residual disease or node positivity.[14]

Statistical Package for the Social Sciences (SPSS) version 23 was used for data processing. Age of the women with breast cancer recruited in study was expressed as mean and standard deviation. Stage of cancer, pathological response seen on histopathology and presence of delays in treatment due to neutropenia or cardiotoxicity were expressed as frequencies and percentages. Pearson Chi-square test and Fischer exact test were applied to assess the association of various clinical factors with pathological response to use of dual HER2 blockade by keeping *p*-value ≤0.05 as significant.

RESULTS

A total of 180 women were made part of this study who were suffering from HER2 positive early or advance breast cancer. Mean age of the patients was 45.56±9.91 years. Table-I summarizes the basic characteristics of participants. Out of 180 patients, 116(32.9%) had complete pathological response while 64(25.6%) had partial response to the neo-adjuvant therapy combined with dual HER2 blockade.

Table-I: Social, Demographic, Clinical and Pathological Profile of Patients (n=180)

Study parameters	values
Age (years)	
Mean+SD	45.56±9.91 years
Pathological Response	
Partial response	64(35.5%)
Complete response	116(64.5%)
Staging of tumor at time of diagnosis	
T1-2N1	118(65.5%)
T4N2	62(34.5%)
Molecular subtypes	
ER PR Her +	105(58.3%)
ER PR- Her +	75(41.7%)
Cardiotoxicity during course of treatment	
No	175(97.2%)
Yes	05(3.8%)
Neutropenia during course of treatment	
No	174(96.6%)
Yes	06(3.4%)

Table-II summarized the results of statistical tests applied to the data collected for this study. Having T1-2N1 disease, ER PR negative and HER2 positive disease and not having interruptions in treatment due to neutropenia or cardiotoxicity were statistically significantly associated with complete pathological response to neo-adjuvant therapy combined with dual

HER2 blockade (*p*-value<0.05) in women enrolled in our study.

Table-II: Pathological Response to Dual HER2 Blockade in Patients of HER2 Positive Early or Advanced Breast Cancer and Clinical Factors Involved (n=180)

Factors	Partial Response n(%)	Complete Response n(%)	*p*-value
Stage of Tumor			
T1-2N1	89(76.7%)	29(45.3%)	<0.001
T4N2	27(23.3%)	35(54.7%)	
Molecular sub types			
ER PR Her +	78(67.2%)	27(42.2%)	0.001
ER PR- Her +	38(32.8%)	37(57.8%)	
Delay in Treatment Due to Cardiotoxicity			
No	116(100%)	59(92.2%)	0.001
Yes	00(0%)	05(7.8%)	
Delay in Treatment Due to Neutropenia			
No	116(100%)	58(90.6%)	<0.001
Yes	00(0%)	06(9.4%)	

DISCUSSION

Dual HER2 blockade, in recent times, is offered routinely to patients with HER2 positive early or advanced breast cancer. Pathological response determines ultimate outcome of any treatment in most cancers, including breast cancer. Chemotherapy remains treatment of choice in neoadjuvent settings but hormonal status of breast tumors provides an additional ground to oncology team to target and achieve complete pathological response. Previously single agents were used for HER2 blockade but recently use of dual blockade is gaining popularity. We conducted this study to analyze response assessment to dual HER2 blockade in HER2 positive early and advanced breast cancer and factors associated with partial response among the study participants.

Chen *et al.*, published a meta-analysis in 2019 regarding efficacy and safety of single and double agent HER2 blockade. They revealed that dual agent blockade was superior in efficacy to single agent HER2 blockade and safety was also not much compromised. No cardiotoxicity was reported in both groups and anemia was seen more in dual agent group.[15] Complete response was seen in a good number of patients in our study, and cardiotoxicity leading to treatment hindrance was seen in only four out of 180 patients. This shows that overall response was good when efficacy and adverse effects were seen as a whole in clinical picture.

Thill *et al.*, concluded that dual blockade of HER2 in HER2 positive breast cancer patients was superior to single agent blockade without much compromise on safety. They advocated use of dual blockade in routine clinical practise.[16] Complete pathological response was seen in majority of patients included in our study. Having T1-2N1 disease, ER PR negative and HER2 positive disease, and not having interruptions in treatment due to neutropenia or cardiotoxicity were factors associated with complete pathological response in our study participants.

Hurvitz *et al.*, found that dual blockade was more effective than single agent blockade or using chemotherapy alone.[17] However, neutropenia was found significantly more in patients who received dual HER2 blockade. Six out of 180 patients in our study had significant neutropenia due to which medication schedule needed to be altered and this was associated with partial response in patients. Three-point four percent patients developed neutropenia, which seems a considerable number but as it was a small study therefore more data on these patients is required from our region in order to have an exact picture of this adverse effect.

Tan *et al.*, studied the impact of addition of dual HER2 blockade in routine chemotherapy in patients of HER2 positive early breast cancer. They concluded that addition of dual blockade provided increased benefit to patients and more complete response was achieved. Safety did not emerge as major concern in their trial.[18] Though our study design was simple, but results supported the findings generated by Tan *et al.*

LIMITATIONS OF STUDY

This was not a randomized controlled trial so exact efficacy and safety of dual HER2 blockade cannot be ascertained. Moreover, the sample size was small and from one oncology unit which is a military setting and does not represent true picture of either private or public sector. Multiple factors could affect pathological response, use of dual HER2 blockade is only one factor. Catering for all the factors in study design may generate better results.

CONCLUSION

Complete pathological response was seen in the majority of patients included in our study. Having T1-2N1 disease, ER PR negative and HER2 positive disease, and not having interruptions in treatment due to neutropenia or cardiotoxicity were factors associated with complete pathological response in our study participants.

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Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

AB & MN: Data acquisition, data analysis, critical review, approval of the final version to be published.

MN & MHB: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

RK & AK: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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