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RESEARCH

Evaluation of clinical and pathological responses of HER-2 positive locally advanced breast cancer patients after neoadjuvant therapy and surgery

HER-2 pozitif lokal ileri meme kanseri hastalarının neoadjuvan tedavi ve cerrahi sonrası klinik ve patolojik yanıtlarının değerlendirilmesi

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Abstract

Purpose: This study aimed to compare the effectiveness and toxicity of neoadjuvant dual Human epidermal growth factor receptor-2 (HER-2) blockade combined with chemotherapy in advanced breast cancer.

Materials and Methods: Patients with HER2-positive breast cancer who received trastuzumab (T)+ pertuzumab (P) with weekly neoadjuvant paclitaxel or docetaxel were included in the study. Patients' age, clinical stage, histological reports, ki-67 index, toxicity profiles, and the state of the pathological and radiological response following neoadjuvant therapy were evaluated.

Results: All 40 patients were women (mean age 50.9) and the overall rate of pathological complete responses was 62.5% (25/40). The rates of non-responsive patients and grade 2 neuropathy were statistically significantly higher in the group receiving P+T+Weekly Paclitaxel. When SUV values were analyzed based on hormone positivity, it was found that they decreased dramatically in both groups and were statistically significant. The logistic regression analysis developed to predict the precise response status to therapy was found to be significant.

Conclusion: When comparing the agents used in dual HER-2 targeted therapies, patient response rates and toxicity profiles may differ. Ductal carcinoma in situ (DCIS) and molecular subtype were found to be significant variables in the developed logistic regression model.

Keywords: Breast cancer, dual blockage, HER2, response rate

Öz

Amaç: Bu çalışmanın amacı, ilerlemiş meme kanserinde neoadjuvan dual insan epidermal büyüme faktörü reseptörü 2 (HER2) blokajında kullanılan kemoterapotiklerin etkinliğini ve toksisitesini karşılaştırmaktı.

Gereç ve Yöntem: Haftalık neoadjuvan paklitaksel veya dosetaksel ile trastuzumab (T)+ pertuzumab (P) alan HER2 pozitif meme kanserli hastalar çalışmaya dahil edildi. Hastaların yaşı, klinik evresi, histolojik raporları, ki-67 indeksi, toksisite profilleri ve neoadjuvan tedavi sonrası patolojik ve radyolojik yanıt durumu değerlendirildi.

Bulgular: Çalışmaya dahil edilen 40 hastanın tümü kadındı (ortalama yaş 50.9) ve genel patolojik tam yanıt oranı %62.5 idi (25/40). Haftalık P+T+Paklitaksel alan grupta tedaviye yanıtsız hasta ve grade 2 nöropati oranları istatistiksel olarak anlamlı derecede yüksekti. SUV değerleri hormon pozitifliğine göre analiz edildiğinde, her iki grupta da önemli ölçüde azaldığı ve istatistiksel olarak anlamlı olduğu bulundu. Tedaviye kesin yanıt durumunu tahmin etmek için geliştirilen lojistik regresyon analizi anlamlı bulunmuştur.

Sonuç: Dual HER-2 hedefli tedavilerde kullanılan ajanlar karşılaştırıldığında hasta yanıt oranları ve toksisite profilleri farklı olabilmektedir. Geliştirilen lojistik regresyon modelinde duktal karsinom in situ (DCIS) ve moleküler alt tipin anlamlı değişkenler olduğu bulunmuştur.

Anahtar kelimeler: Meme kanseri, dual blokaj, HER2, yanıt oranı

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INTRODUCTION

Breast cancer is highly metastatic and the most common malignancy in women. It is a heterogeneous disease with different clinical characteristics and molecular phenotypes. 15-20% of breast cancer patients have overexpression of the human epidermal growth factor receptor 2 (HER-2)[1,2].

HER-2, which is present on the surface of certain cancer cells, regulates cell growth, division, and survival. As a result, aggressive tumor behavior is associated with HER2 overexpression. Treatments for breast cancer and other cancers use HER2-targeted drugs. Monoclonal antibodies, small molecules, and other medicines that target CerbB2 by binding to the HER-2 receptor or inhibiting the HER-2 signaling pathway belong to this category[3,4].

Paclitaxel and Docetaxel are important chemotherapy drugs used in the treatment of breast cancer and are often part of a comprehensive treatment plan aimed at improving patient outcomes. The use of a monoclonal antibody called trastuzumab in combination with conventional chemotherapy has resulted in higher clinical response and survival rates[5,6].

Trastuzumab is a monoclonal antibody developed against the epitope of the HER-2 receptor on the cell surface. Trastuzumab inhibits tumor growth by a variety of processes, which are still being studied. Trastuzumab has been reported to have anticancer effects includingthat it may cause antibody-dependent cellular cytotoxicity; inhibits angiogenesis inhibit HER-2 driven signaling cascades, and induce apoptosis[7].

Pertuzumab is a monoclonal antibody that binds to the extracellular part of the HER-2 receptor and inhibits receptor dimerization, ligand binding-induced signal transduction, and heterodimerization of HER-2 with other EGFR family members[8,9].

Dual HER-2 blockade is a therapeutic strategy that specifically targets the HER2 protein in cancer cells using two different drugs. Multiple researches have shown that neoadjuvant dual HER-2 blockage using trastuzumab and pertuzumab in combination with chemotherapy gives better results. Dual HER-2 blockade has become the accepted neoadjuvant approach for HER2-positive breast cancer[10,11]. However, there are still incidences of drug resistance following therapy[12].

This study compared the use of docetaxel and paclitaxel in dual HER-2 blockade for the treatment of breast cancer patients. The specific efficacy and toxicity characteristics of two chemotherapeutic drugs that operate through comparable pathways and are utilized in neoadjuvant dual HER-2 inhibition combined with chemotherapy in advanced breast cancer are the focus of our research.

MATERIALS AND METHODS

Sample

This research was designed as a retrospective cohort study involving 40 locally advanced breast cancer patients who received neoadjuvant Paclitaxel or Docetaxel with trastuzumab (T)+ pertuzumab (P) was conducted between January 2017 and December 2022 in the Oncology department of the Balcalı Hospital of Cukurova University. In the sample size analysis, which was accepted as effect size (d)=0.25 power 80%, type 1 error=0.01, the number to be reached was found to be 40.

Between 2017 and 2022, 300 patients with locally advanced breast cancer who were newly diagnosed and evaluated in the oncology outpatient clinic were scanned from the polyclinic automation and information processing system. Among these newly diagnosed breast cancer patients, 65 patients with Her-2 (++) and FISH positive and Her-2 (+++) were identified. Forty patients with Her-2 positive and locally advanced stage were included in the study. Information about the patients was obtained from patient files and hospital registry system medical records. The laboratory values of the patients, pet-CT radiological imaging for staging, the chemotherapy regimens they received, the surgical operation performed, and the pathological results obtained were obtained from this database.

Patients with positive HER-2 receptor status (+++) and those who were diagnosed with locally advanced or early-stage breast cancer (with a tumor size less than 2 cm in radiological evaluation) were included. The study was open to adult patients aged 18 years and above who had not received any previous chemotherapy treatment. Patients who expressed their willingness to adhere to the recommended chemotherapy regimen were also considered for participation.

Patients with negative HER-2 receptor status or HER-2 receptor overexpression (+) along with

negative FISH test results were excluded. Patients with advanced disease or those who had undergone surgical intervention did not meet the inclusion criteria. The presence of severe hepatic or renal failure also led to exclusion from the study. Moreover, individuals with active heart disease or stage 3-4 heart failure, as well as those with immunodeficiency or neuropsychiatric disorders that could potentially interfere with chemotherapy treatment, were not considered. Patients declining to adhere to the recommended chemotherapy regimen and those with a secondary malignant disease were excluded. Lastly, individuals with an ECOG performance status greater than 2 did not meet the study's inclusion criteria.

Procedure

The study was conducted after receiving approval from the Cukurova University Clinical Ethical Board (No: 131:12, 10.03.2023). The patients' factors such as age, gender, tumor grade, Ki-67 proliferation index, neoadjuvant treatment regimen, and histological subtype of the tumor were evaluated in addition to their response and side effects after neoadjuvant treatment. Immunohistochemical analysis of biopsy samples taken from the patients before neoadjuvant treatment was used in determining their CerbB2 status. Paraffin blocks for CerbB2 immunohistochemical staining 4 micrometer thick sections were prepared. Using the immunohistochemical method, sections were taken on positively charged slides. For CerbB2 antibody breast cancer tissue was used as a control block.

Tumor size measurement is based on pathology, patients with negative status were excluded because the treatments used in this study have been applied in HER-2 positive patients in the literature.

Patients received weekly paclitaxel (80 mg/m^2) for 12 weeks or docetaxel (75 mg/m^2, escalating, if tolerated, to 100 mg/m^2) every 3 weeks for 4 cycles with trastuzumab (8 mg/kg loading dose followed by 6 mg/kg) and pertuzumab (840 mg loading dose followed by 420 mg) every 3 weeks from the start of taxane.

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) software (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY) was used for data analysis, with data presented in numerical, percentage, arithmetic mean, standard deviation, and median formats. The Kolmogorov-Smirnov test was used as a normality test. Parametric tests were used for normally distributed data, while non-parametric tests were used for data that did not meet parametric assumptions. Paired t-test, Wilcoxon test, Chi-square test, and Binary logistic regression analysis were used for statistical analysis. A p-value of less than 0.05 was considered statistically significant. The Chi-square test was applied to assess associations between categorical variables like age, gender, treatment response, and side effects. For ordinal variables such as tumor grade, we employed the Wilcoxon rank-sum test.

RESULTS

40 breast cancer patients participated in the study and the average age was 50.98 years. The most common pathological subtype in patients is invasive ductal carcinoma. 72.5% of the tumors are grade 3, 55% have vascular and 37.5% have neural invasion. The distribution of the clinical characteristics of the patients is given in Table 1.

The rates of grade 2 neuropathy and non-responding patients were found to be statistically significantly higher in the group receiving weekly Per + T + Paclitaxel therapy in the comparison between the side effects of drugs and the response to treatment (effectiveness) with the neoadjuvant chemotherapy regimen (Table 2). When comparing the side effects and effectiveness (treatment response) of medications based on hormonal status, no statistically significant differences were found between the groups (Table 3).

When comparing the primary and final SUV (Standardized Uptake Value) values according to drug group and hormone positivity, it was found that both the Per+T+Docetaxel and Per+T+weekly Paclitaxel groups showed a significant decrease in SUV values with a large effect size. When examined based on hormone positivity, a decrease in SUV values was observed, which was statistically significant (Table 4).

Logistic regression analysis created to predict the exact response to treatment was important (omnibus test p=0.017). Independent variables included in the model are age, Ki 67, vascular invasion, neural invasion, CERBB2, carcinoma in situ (DCIS), histology type, and molecular type. It was found that DCIS and molecular type were important among the

variables included in the model, the probability of complete response was 8.76 times higher in the presence of in situ, and 6.24 times higher in the ER(-) PR(-) HER2 (+) sub-molecular type (Table 5).

Table 1. Clinical and histopathological characteristics of patients.

Variables	**n(%) or X±S.D.**
Age	50.98±13.18
Pathology	
IDC	32 (80.0)
ILC	4 (10.0)
Other	1 (2.5)
TC	2 (5)
PC	1 (2.5)
GRADE	
Grade 2	11 (27.5)
Grade 3	29 (72,5)
Ki-67	47.57±18.49
Vascular Invasion	
Yes	16 (40)
No	22 (55)
Unknown	2 (5)
Neural Invasion	
Yes	23 (57.5)
No	15 (37.5)
Unknown	2 (5)
ER %	43.75±43.21
PR %	12.08±23.709
CERBB2 status	
2 ++, FISH+	11 (27.5)
3 +++	29 (72.5)
Molecular Type	
Luminal B, HER2 (+)	23 (57.5)
ER(-) PR(-) HER2 (+)	17 (42.5)
DCIS	
No	25 (62.5)
Yes	15 (37.5)
Diagnosis Stage	
Locally advanced	32 (80)
Early Stage	8 (20)
Localization	
Right	21 (52.5)
Left	19 (47.5)
MRI	
Multicentric	11 (27.5)
Multifocal	17 (42.5)
Unifocal	12 (30)
Neoadjuvant CT	
Per+T+ Docetaxel	31 (77.5)
Per+T+Haftalık Paclitaxel	9 (22.5)
Hospitalization	
Yes	37 (92.5)
No	3 (7.5)
Surgery	
Tm+Ad (Mrm)	11 (27.5)
Tm+Slnb	29(72.5)
Number of lymph node	
<4	6 (15)

4-10	24 (60)
>10	10 (25)
Number of positive lymph node	1.92±5.03
PET response	
Complete response	31 (77.5)
Partial response	9 (22.5)
Pathological response	
Complete response	25 (62.5)
Partial response	10 (25)
No response	5 (12.5)
Adjuvant CT	
Pertuzumab + Trastuzumab	2 (5)
Trastuzumab	33 (82.5)
Tdm-1	5 (12.5)

IDC, Invasive Ductal Carcinoma; ILC, Invasive Lobular Carcinoma; TC, tubular carcinoma PC, papillary carcinoma; DCIS, Ductal Carcinoma in Situ; Per, Pertuzumab

Table 2. Comparison of side effects and effectiveness according to neoadjuvant chemotherapy regimen

		Neoadjuvant Chemotherapy n(%)		
Side effect	**GRADE**	**Per+T+Docetaxel**	**Per+T+ Paclitaxel**	**p**
Neuropathy	0	13 (41.9)	0 (0)	**<0.001**
	1	16 (51.6)	3 (33.3)	
	2	2 (6.5)	6 (66.7)	
Anemia	0	8 (25.8)	1 (11.1)	0.452
	1	16 (51.6)	7 (77.8)	
	2	7 (22.6)	1 (11.1)	
Thrombocytopenia	0	18 (58.1)	4 (44.4)	0.161
	1	8 (25.8)	5 (55.6)	
	2	5 (16.1)	0 (0)	
Leukopenia	1	10 (32.3)	8 (88.9)	0.014
	2	18 (58.1)	1 (11.1)	
	3	3 (9.7)	0 (0)	
Neutropenia	1	15 (48.4)	8 (88.9)	0.123
	2	14 (45.2)	1 (11.1)	
	3	2 (6.5)	0 (0)	
Nausea	0	3 (9.7)	0 (0)	0.704
	1	16 (51.6)	7 (77.8)	
	2	10 (6.5)	2 (22.2)	
	3	2 (6.5)	0 (0)	
Mucositis	0	6 (19.4)	1 (11.1)	0.504
	1	14 (45.2)	7 (77.8)	
	2	10 (32.3)	1 (11.1)	
	3	1 (3.2)	0 (0)	
Fatigue	0	5 (16.1)	3 (33.3)	0.472
	1	14 (45.2)	5 (55.6)	
	2	11 (35.5)	1 (11.1)	
	3	1 (3.2)	0 (0)	
Diarrhea	0	26 (83.9)	6 (66.7)	0.472
	1	4 (12.9)	3 (33.3)	
	2	1 (3.2)	0 (0)	
Rash	0	22 (71.0)	6 (66.7)	0.762
	1	8 (25.8)	3 (33.3)	
	2	1 (3.2)	0 (0)	
Increase in ALT	0	14 (45.2)	6 (66.7)	0.352
	1	15 (48.4)	2 (22.2)	
	2	1 (3.2)	1 (11.1)	

	3	1 (3.2)	0 (0)	
Vomiting	0	2 (6.5)	2 (22.2)	0.387
	1	16 (51.6)	5 (55.6)	
	2	8 (25.8)	2 (22.2)	
	3	5 (16.1)	0 (0)	
Alopecia	No	1 (3.2)	2 (22.2)	0.121
	Yes	30 (96.8)	7 (77.8)	
Headache	No	13 (41.9)	3 (33.3)	0.717
	Yes	18 (58.1)	6 (66.7)	
Myalgia	No	5 (16.1)	2 (22.2)	0.645
	Yes	26 (83.9)	7 (77.8)	
Febrile Neutropenia	No	19 (61.3)	6 (66.7)	1.000
	Yes	12 (38.7)	3 (33.3)	
	Treatment response			
PET response	Complete response	26 (83.9)	5 (55.6)	0.168
	Partial response	5 (16.1)	4 (44.4)	
Pathological Response	Complete response	22 (71)	3 (33.3)	**0.039**
	Partial response	7 (22.6)	3 (33.3)	
	No response	2 (6.5)	3 (33.3)	

Per, Pertuzumab; T, Trastuzumab

Table 3. Comparison of side effects and treatment effectiveness according to hormone status

		Hormone Status (CERB2)		
Side effect	**Grade**	**++ Positive ve FISH +**	**+++ Positive**	**p**
Neuropathy	0	3 (27.3)	10 (34.5)	0.330
	1	4 (36.4)	15 (51.7)	
	2	4 (36.4)	4 (13.8)	
Anemia	0	3 (27.3)	6 (20.7)	0.702
	1	7 (63.6)	16 (55.2)	
	2	1 (9.1)	7 (24.1)	
Thrombocytopenia	0	7 (63.6)	15 (51.7)	0.421
	1	4 (36.4)	9 (31)	
	2	0 (0)	5 (17.2)	
Leukopenia	1	6 (54.5)	12 (41.4)	0.662
	2	5 (45.5)	14 (48.3)	
	3	0 (0)	3 (10.3)	
Neutropenia	1	7 (63.6)	16 (55.2)	1.000
	2	4 (36.4)	11 (37.9)	
	3	0 (0)	2 (6.9)	
Nausea	0	0 (0)	3 (10.3)	0.662
	1	6 (54.5)	17 (58.6)	
	2	4 (36.4)	8 (27.6)	
	3	1 (9.1)	1 (3.4)	
Mucositis	0	0 (0)	7 (24.1)	0.258
	1	7 (63.6)	14 (48.3)	
	2	4 (36.4	7 (24.1)	
	3	0 (0)	1 (3.4)	
Fatigue	0	2 (18.2)	6 (20.7)	0.928
	1	5 (45.5)	14 (48.3)	
	2	4 (36.4)	8 (27.6)	
	3	0 (0)	1 (3.4)	
Diarrhea	0	9 (81.8)	23 (79.3)	1.000
	1	2 (18.2)	5 (17.2)	
	2	0 (0)	1 (3.4)	
Rash	0	8 (72.7)	20 (69)	1.000
	1	3 (27.3)	8 (27.6)	

	2	0 (0)	1 (3.4)	
Increase in ALT	0	7 (63.6)	13 (44.8)	0.519
	1	3 (27.3)	14 (48.3)	
	2	1 (9.1)	1 (3.4)	
	3	0 (0)	1 (3.4)	
Vomiting	0	0 (0)	4 (13.8)	0.291
	1	5 (45.5)	16 (55.2)	
	2	5 (45.5)	5 (17.2)	
	3	1 (9.1)	4 (13.8)	
Alopecia	No	0 (0)	3 (10.3)	0.548
	Yes	11 (100)	26 (89.7)	
Headache	No	4 (36.4)	12 (41.4)	1.000
	Yes	7 (63.6)	17 (58.6)	
Myalgia	No	3 (27.3)	4 (13.8)	0.369
	Yes	8 (72.7)	25 (86.2)	
Febrile Neutropenia	No	8 (72.7)	17 (58.6)	0.486
	Yes	3 (27.3)	12 (41.4)	
	Treatment response			
PET response	Complete response	7 (63.6)	24 (82.8)	0.227
	Partial response	4 (36.4)	5 (17.2)	
Pathological Response	Complete response	5 (45.5)	20 (69)	0.448
	Partial reponse	4 (36.4)	6 (20.7)	
	No response	2 (18.2)	3 (10.3)	

Table 4. SUV comparison according to drug and hormone positivity

	PRIMER SUV		Last SUV			
Treatment	X±S.D.	Median	X±S.D.	Median	p	E.S.
Per+T+Docetaxel	12.875±5.750	13.5	2.65±2.412	2.5	<0.001	0.992
Per+T+weekly Paclitaxel	12.484±4.224	12.5	3.258±2.002	3.5	0.009	1.000
CERBB2						
2 ++FISH	12.536±4.98	10.5	3.59±3.850	2.3	0.004	1.00
3 +++	12.882±5.625	13.5	2.49±1.353	2.5	<0.001	0.991

SUV, Standardized Uptake Value; Per, Pertuzumab; T, Trastuzumab

Table 5. Logistic regression analysis for prediction of complete response

		B	p	OR	95% CI for OR	
					Lower	Upper
Step 1[a]	DCIS	1.686	0.021	5.400	1.291	22.596
	Constant	0.255	0.484	1.291		
Step 2[b]	DCIS	2.171	0.014	8.769	1.550	49.625
	Molecular Type	1.831	0.041	6.241	1.079	36.113
	Constant	0.372	0.353	1.451		

B, beta coefficients; OR, odds ratio; Cl, confidence interval

Table 6. Concordance between PET and pathologic evaluation.

Ratios	100.0 %
Sensitivity	60.0 %
Specificity	85.0 %
Accuracy	62.5 %
Prevalence	80.6 %
Positive Predictive Value	100.0 %
Negative Predictive Value	80.6 %
Post-test Disease Probability	100.0 %
Post-test Health Probability	2.50
Positive Likelihood Ratio	0.00
Negative Likelihood Ratio	

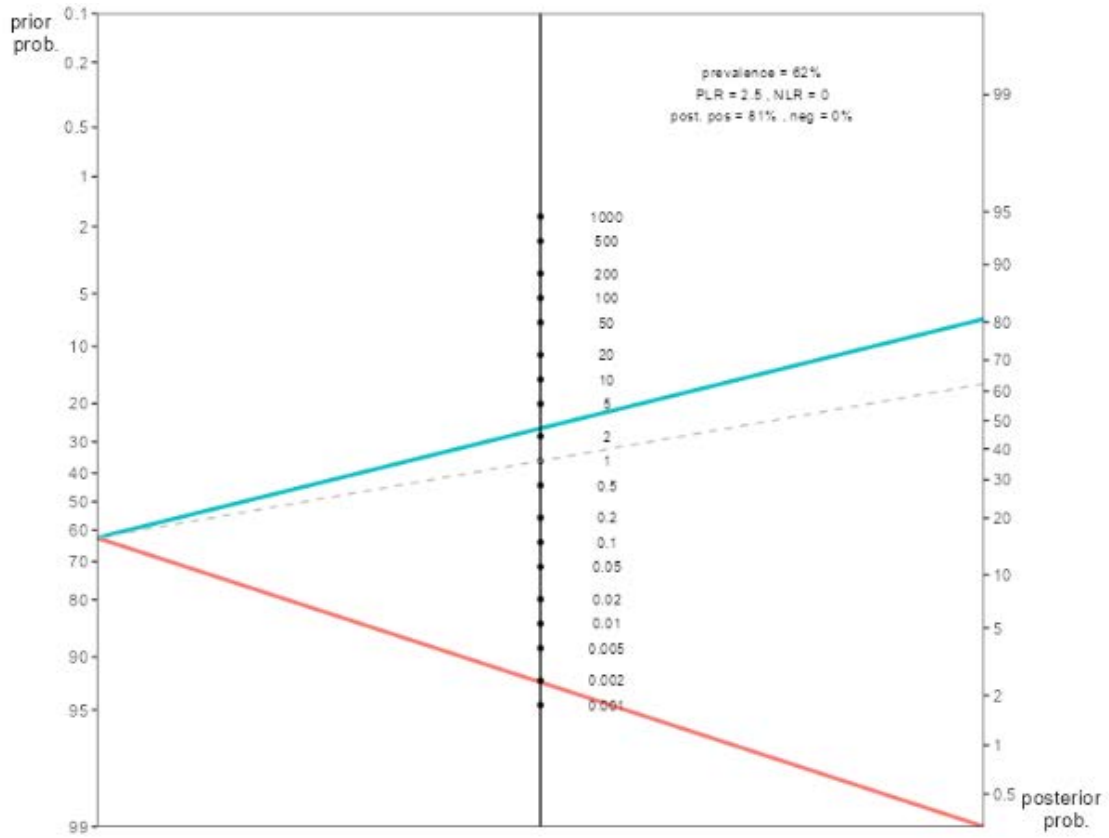

Figure 1. The concordance between PET and pathological evaluation

DISCUSSION

In our study, the research gap we aim to address revolves around the specific efficacy and toxicity aspects of two chemotherapeutic agents working through similar mechanisms used in neoadjuvant dual HER-2 blockade combined with chemotherapy in advanced breast cancer. Our study objectives are to explicitly compare the efficacy and toxicity profiles of neoadjuvant dual HER-2 blockade combined with chemotherapy in advanced breast cancer patients. We seek to determine the response rates, potential side effects, and overall outcomes resulting from this treatment approach. We hypothesize that dual HER-2 blockade in combination with chemotherapy will lead to better response rates and manageable toxicity profiles compared to alternative treatment strategies. By systematically evaluating these factors, we aim to add valuable information to the optimization of advanced breast cancer treatment regimens and ultimately improve patient outcomes and quality of life. We found that the rates of non-responsive patients and grade 2 neuropathy are different in the two drug groups, also based on hormone positivity SUV values decreased dramatically in both groups.

Several neoadjuvant studies showed an approximate increase in pathological complete response, but the rates differ considerably amongst these studies. The basis of the chemotherapy regimen, tumor size, the course of therapy, and ER status are all potential causes[13-15].

To find specific markers that may help predict which patients will respond to HER2-targeted therapy the best, a number of neoadjuvant trials have been conducted. For instance, many studies investigated the relationship between ER status and pathological complete response rate. The findings could then show that individuals with ER-negative status had higher complete response rates[13].

Trastuzumab binds to the HER-2 receptor on the surface of HER2-positive cancer cells, preventing the excessive growth and proliferation of cancer cells and supporting the strengthening of the immune response against cancer cells. Pertuzumab binds to the HER2 receptor on the surface of HER-2-positive cancer cells at a different site. This prevents the formation of heterodimers between the HER2 receptor and other epidermal growth factor receptors, allowing the cancer cell to transmit growth signals less effectively[16].

Combining drugs that target the HER family and function complementarily is a technique to combat drug resistance. Combinations of anti-HER drugs have shown synergistic effects in several preclinical investigations, which may also assist in combating trastuzumab resistance[13].

Using trastuzumab and pertuzumab together aims to interfere more effectively with HER2-positive cancer cells. Since both drugs act by binding to different parts of the HER2 receptor, this combination treatment can more comprehensively suppress the HER2 signaling pathways of cancer cells[16].

HER-2 dual blockade reduces the likelihood of developing resistance to treatment and increases the chances of patients responding better to treatment. However, there are also some points of controversy regarding the HER-2 dual blockade. Combination therapy may require a more complex treatment regimen due to factors such as cost and side effects[17]. Furthermore, as each patient is different and the effectiveness of the combination of both drugs may vary depending on individual factors, treatment decisions should be made taking into account the patient's situation.

Wang et al.[18] reviewed randomized trials which involved a total of 2758 patients who use dual HER2 blockade in neoadjuvant treatment for HER2+ breast cancer. The meta analysis showed a statistically significant difference between single-agent treatment and dual HER2-blockade treatment. Furthermore, there was not a statistically significant distinction in the frequency of major side effects, and the hormone receptor status did not affect the percentage of pathologic complete responses. In our study, there were no statistically significant differences between the groups when evaluating the adverse reactions and effectiveness (treatment response) of drugs based on hormonal status, but statistically significant a decrease ($p<0.001$ for the Docetaxel group, $p=0.009$ for the Paclitaxel group) in SUV values.

The concordance between PET and pathological evaluation in neoadjuvant treatment response (Table 6) in breast cancer was assessed using the Fagan Nomogram (Figure 1). The positive likelihood ratio is calculated to be 2.50. It could imply that the positive result is of moderate strength to confirm the condition. However, it is critical to assess this value in light of the clinical setting and disease incidence.

A negative likelihood ratio of 0.00 indicates that the probability of individuals receiving a negative test result carrying the disease is nearly zero; however, in some cases, this value may not be practically 0 because of the small sample size or methodological factors that may attract the negative probability ratio to low but non-zero values.

The most important limitation of this study is that it was single centered and the number of patients was limited. In conclusion, patient response rates and toxicity profiles may differ when comparing agents used in dual HER-2 targeted therapies. Therefore, future studies with larger and more comprehensive patient groups are expected to provide more comprehensive information about the efficacy and safety of the treatment. Future large-scale studies will help us to better understand the effects of dual blockade therapy on larger patient populations.

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Patient consent for publication: The patient signed an informed consent form after being informed of its details.

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