Chemotherapy Choice in Neoadjuvant Dual Her2 Blockade; Is It Really Necessary to Add Anthracycline?

Ahmet Ozveren (ahmet_ozveren@yahoo.com)
Izmir Private Kent Hospital
Atike Erdogan
Manisa Celal Bayar Üniversitesi Hafsa Sultan Hastanesi
Ferhat Ekinci
Manisa Celal Bayar Üniversitesi Hafsa Sultan Hastanesi
Kutay Kirdok
Manisa Celal Bayar Üniversitesi Hafsa Sultan Hastanesi
Elvina Almuradova
Ege Üniversitesi Tıp Fakültesi Hastanesi
Bulent Karabulut
Izmir Private Kent Hospital

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Abstract

1. Background

Addition of trastuzumab and pertuzumab to neoadjuvant chemotherapy in HER-2 positive patients is the current clinical standard today. In studies on neoadjuvant chemotherapy, the primary endpoint is pathological complete response (pCR). The aim of our study is to answer the following questions: Does the anthracycline containing chemotherapy which will be used alongside dual HER-2 blockade in neoadjuvant treatment has additional benefit?

2. Methods

52 patients with HER-2 positive breast cancer who received neoadjuvant chemotherapy were retrospectively evaluated. Three centers participated in the study (İzmir Kent Hospital, Manisa Celal Bayar University, Ege University). The effects of chemotherapy regimen and several other factors such as age, stage, menopause status, lymph node positivity, hormone receptor positivity on pCR were evaluated. All methods were performed in accordance with the relevant guidelines and regulations.

3. Results

The mean age of diagnosis was 46 ± 9 (range: 26-67). The pCR rate was 71.2% (37) in the entire study group. In terms of pCR, no significant difference between those who use an anthracycline containing and non-anthracycline containing regimens (71.4% vs 70%, p=1.000), those with negative and positive hormone receptors (64.7% vs 74.3%, p=0.525), and Ki67 levels of %20 or less and those over 20% (60% vs 73.8%, p=0.447), premenopausal and postmenopausal ones (76.9% vs 65.4%, p=0.054).

4. Conclusions

As a result of the data we obtained, it was concluded that adding anthracycline regimen to dual HER-2 blockade in the neoadjuvant period did not bring additional benefits in terms of pCR. Additional studies are needed on whether the use of anthracycline-containing regimen contributes additionally in patients who will use the neoadjuvant pertuzumab-trastuzumab combination.

Introduction

Human epidermal growth factor receptor 2 (HER-2) is a tyrosine kinase transmembrane receptor and shows positivity in 15-20% of breast cancer cases.[1] HER-2 positivity is associated with aggressive course and poor prognosis.[2] Dual HER-2 blockade has proven its benefit firstly in metastatic HER-2 positive disease and then in the neoadjuvant stage. [3–5]

The addition of trastuzumab and pertuzumab to neoadjuvant chemotherapy in HER-2 positive patients is now the clinical standard. The main purpose of neoadjuvant therapy is to increase breast protection rates by obtaining downstage in the tumor.[6] In studies on neoadjuvant chemotherapy, the primary endpoint is pathological complete response (pCR). Pathological complete response has a prognostic determinant role.[7] pCR was found to be associated with an increase in survival.[8] In neoadjuvant chemotherapy, dual HER-2 blockade led to an increased pathological complete response.[9] In the BERENICE study, dual HER-2 blokage with neoadjuvant chemotheraphy resulted in pCR rates up to 75% in HER-2 enriched group with.[3]

The aim of our study is to answer the following questions: Does the anthracycline containing chemotherapy which will be used alongside dual HER-2 blockade in neoadjuvant treatment has additional benefit? Does cardiotoxicity increase with dual HER-2 blockade after anthracycline? To answer these questions, we retrospectively evaluated patients who received dual HER-2 blockade in neoadjuvant therapy and their responses according to the chemotherapy regimen they received.

Materials And Methods

The present study was approved by the Manisa Celal Bayar University Faculty of Medicine ethics committee board and was exempted from informed consent requirements owing to its retrospective design. After receiving the ethical approval from the Medical Research Ethics Committee of the Manisa Celal Bayar University Faculty of Medicine with the number 99 dated 24.08.2020, clinical characteristics, chemotherapy regimens, laboratory data, pCR rates and echocardiography results of 52 patients who were given pertuzumab-trastuzumab dual HER-2 blockades in neoadjuvant therapy in 3 clinical centers (Izmir City Hospital, Manisa Celal Bayar University, Ege University) in the last 3 years were examined retrospectively. All methods were performed in accordance with the relevant guidelines and regulations.

In the immunohistochemistry (IHC) analysis, those with estrogen reseptor (ER) or progestreone reseptor (PR) positivity were classified as hormone receptor positive. Tumors with ER and PR negativity were classified as hormone receptor negative. Those with +3 with HER-2 IHC analysis and those who tested positive for HER-2 Fluorescence in situ hybridization (FISH) were considered HER-2 positive.

Patient file scanning for neoadjuvant therapies revealed that 52 patients used 2 different chemotherapy regimens. 1st chemotherapy regimen: dose dense adriamisin-cyclophosphamide followed by weekly paclitaxel with trastuzumab-pertuzumab; (Anthracycline 60 mg/m2 and cyclophosphamide 600 mg/m2 were applied once in every 14 days for 4 cycles, then paclitaxel 80 mg/m2 was used for 12 weeks along with trastuzumab (6 mg/kg maintenance dose after 8 mg/kg loading dose) and pertuzumab(420 mg maintenance dose after 840 mg loading dose) which were used once in every 21 days), 2nd chemotherapy regimen: docetaksel-carboplatin-trastuzumab-pertuzumab (TCHP); Dosetaxel 75 mg/m2, carboplatin 6 AUC, trastuzumab (6 mg/kg maintenance dose after 8 mg/kg loading dose) and pertuzumab (420 mg maintenance dose after 840 mg loading dose); all of which were used once in every

21 days. Within the scope of the Turkish Health Ministry reimbursement, pertuzumab was used as only 4 cycles in both regimens.

Pathological complete response is considered ypT0/is,N0. Clinical and pathological staging was performed according to the American Joint Commitee of Cancer classification.[10]

Statistical analysis

Factors that may affect pCR (such as age, menopausal condition, clinical stage, histological grade, hormone receptor status, chemotherapy regimen) were examined by univariate logistic regression models. Odds ratio for all potential predictors was evaluated with a 95% safety interval and pCR response was evaluated. In multiple analyses, the p value below 0.050 was considered statistically significant. The distribution balance between groups was evaluated by skewnes method. SPSS 21 was used for statistical analysis.

Results

The height, weight and laboratory data of the patients at admission are shown in Table 1. The mean age of the included 52 patients at diagnosis was 46 ± 9 (range: 26-67).

Table 1
Age, height, weight and laboratory data of the subjects at admission.

	Minimum	Maximum	Mean	Std. Deviation
Age	26.0	67.0	46.0	9.4
Height in cm	145.0	175.0	160.0	7.0
Weight in Kg	42.0	116.0	68.0	14.0
ALT	7.0	75.0	19.0	13.0
AST	8.0	45.0	18.0	7.8
Albumin	4.0	5.2	4.5	0.3
Total Biluribin	0.1	1.0	0.4	0.2
Creatinine	0.5	0.9	0.7	0.1
GFR	76.0	124.0	102.0	13.4
Calcium	8.8	10.6	9.6	0.4
CRP	0.1	4.8	0.8	1.1
CEA	0.6	26.0	4.1	4.7
CA 15-3	1.2	74.7	26.1	16.7
Hemoglobin	9.8	15.1	12.8	1.3
Platelet	206000.0	442000.0	300038.0	60741.0
Neutrophil	1960.0	7560.0	4340.0	1411.0
Lymphocyte	620.0	7310.0	2214.0	1099.0
MPV	7.5	11.7	9.9	0.9
NLR	0.6	6.1	2.3	1.1
PLR	33.8	440.3	164.1	83.7

Table 2 shows the patient distribution according to chronic illness, Eastern Cooperative Oncology Group (ECOG) performance status, tumor multifocality, tumor category (T), lymph node involvement, tumor stage, surgical method, histological grade, side efect of cardiotoxicity.

Table 2
Patient distribution according to chronic illness, ECOG, side effect of cardiotoxicity and tumor related factors.

	Count	Percent
Chronic illness		
Present	20	38.50%
Absent	32	61.50%
ECOG		
0	42	80.80%
1	9	17.30%
2	1	1.90%
Stage at diagnosis		
1	1	1.90%
2	7	13.50%
3	44	84.60%
Localisation of tumor		
Right	24	46.20%
Left	24	46.20%
Bilateral	4	7.0%
T category		
T1	10	19.20%
T2	27	51.90%
T3	12	23.10%
T4	3	5.80%
Lymph node status		
N0	0	0%
N1	19	36.50%
N2	24	46.20%
N3	9	17.30%

	Count	Percent
Histological grade		
gr1	0	0%
gr2	23	44.20%
gr3	29	55.80%
Multifocality		
Present	25	48.10%
Absent	27	51.90%
Type of surgery		
Partial mastectomy	33	63.50%
Total mastectomy	19	36.50%
Cardiotoxicity		
Present	3	5.80%
Absent	49	94.20%

While 80.8% (42) of the patients received anthracyclines, 19.2% (10) had chemotherapy regimens containing platinum. 50% of the patients (26) were premenopausal in diagnosis, 84.6% (44) had stage 3 tumor, 15.4% (8) had stage 1 or 2 tumor. 32.7% (17) of the patients were negative for hormone receptors. In 80.8% (42) of the patients, Ki67 was over 20%.

Table 3 shows pathological response status in relation to chemotheraphy regimen, Ki67 level, patient age, menopausal status, lymph node status,hormon receptor status and stage of tumor.

Table 3
Pathological response status in relation to several variables.

	Count (% in column)	Pathological response		P
		Presence of Residuals(% in row)	pCR (%in row)	
Chemotheraphy regimen				1.000
Antracycline	42(80.80%)	12(28.6%)	30(71.4%)	
Platine	10(19.20%)	3(30%)	7(70%)	
Ki67				**0.447**
≤%20	10(19.20%)	4(40%)	6(60%)	
>%20	42(80.80%)	11(26.2%)	31(73.8%)	
Age				**0.021**
<40	16(30.80%)	1(6.2%)	15(93.8%)	
≥40	36(69.20%)	14(38.9%)	22(61.1%)	
Menopause				0.054
Present	26(50.00%)	9(34.6%)	17(65.4%)	
Absent	26(50.00%)	6(23.1%)	20(76.9%)	
Lymph node status				**0.004**
N1	19(36.50%)	1(5.3%)	18(94.7%)	
N2-3	33(63.50%)	14(42.4%)	19(57.6%)	
Category T				0.339
T1	10(19.2%)	4(40%)	6(60%)	
T2	27(51.9%)	9(33.3%)	18(66.7%)	
T3	12(23.1%)	1(8.3%)	11(91.7%)	
T4	3(5.8%)	1(33.3%)	2(66.7%)	
Hormone receptor status				0.525
ER or PR +	35(67.30%)	9(25.7%)	26(74.3%)	
ER and PR -	17(32.70%)	6(35.3%)	11(64.7%)	
Stage at diagnosis				0.412

	Count (% in column)	Pathological response		P
		Presence of Residuals(% in row)	pCR (%in row)	
1-2	8(15.40%)	1(12.5%)	7(87.5%)	
3	44(84.60%)	14(31.8%)	30(68.2%)	
Total	52(100%)	15(28.8%)	37(71.2%)	

The overall pCR rate was 71.2% (37) and pCR was 71.4% (30) in the group that used anthracycline containing regimen and 70% (7) in the group that used TCHP regimen(p=1.000). In patients with breast cancer who received dual HER-2 blockades, it was found that using a regimen containing anthracycline in addition to neoadjuvant therapy did not affect pCR.

pCR in premenopausal patients was 76.9% (20), while the pCR in postmenopausal patients was 65.4% (17), menopausal status was found not to affect pCR (p:0.54). In premenopausal or postmenopausal patients, taking a regimen containing anthracyclines did not contribute to pCR(p>0.050).

pCR was significantly higher in those under 40 years of age (93.8% vs 61.1%, p=0.02). 87.5% of patients under 40 had a regimen containing anthracycline, compared to 77.8% in the over-40s. (p:0.705).

According to the TNM classification, the pCR was 94.7% in those with clinically N1 and 57.6% in those with N2-3 (p:0.004)(Table 3) 68.4% of N1 people received an anthracycline containing regimen, while 87.9% of N2-3 ones received regimen containing anthracycline(p=0.142).

In the group with a Ki67 index below 20%, the pCR was 60%, while in the group above 20%, the pCR was 73.8%(p=0.447).

In the group with negative hormone receptors, pCR was 64.7%, while pCR was 74.3% in the group with positive hormone receptor. The difference was not statistically significant. (p:0.525)

pCR was 68.2% in those with stage 3 disease at the time of diagnosis, while pCR was 87.5% in those with stage 1-2 disease. The difference was not statistically significant (p=0.412). In those with stage 3 disease, regimens containing anthracycline were 81.8% and in those with stage 1-2 it was 75% (p=0.642).

While the rate of patients with cardiotoxicity with dual blockade was 5.8% (3), all these 3 patients were under 65 years of age and used anthracycline containing regimen as well as dual HER-2 blokage as adjuvant. HER-2 blockade was terminated in these patients as soon as the detection of cardiotoxicity.

Discussion

In HER-2 + Stage 4 breast cancer, higher pCR rates were reported with the use of double HER-2 blokage during the neoadjuvant period than previously achieved.[3, 4] The pathological complete response

obtained after neoadjuvant treatment has been shown to be a positive prognostic factor.[10, 11] In the BERENICE study, in the HER2 enriched group, high pCR rates were obtained with the regime containing anthracycline followed by dual her2 blockade, which in turn caused the need to evaluate the additional advantages and possible side effects of anthracycline-containing regimens.[3]

In the TRAIN 2 study, there was no significant difference between the regimen containing anthracyclines and the regimen that did not, and it was reported that it was preferable not to use anthracyclines.[13] The pathological complete response rates obtained in our study was found to be similar in anthracycline containing and not containing regimen groups. All patients with cardiotoxicity (5.8%) were patients who had received the treatment regimen containing anthracycline. The regimen containing the anthracyline preferred in the TRAIN 2 study was different from the one preferred in our study. In addition, in the TRAIN 2 study patients recieved 9 cycles of HER2 dual blockade, in our study it was limited to 4 cycles in accordance with the restriction of the Turkish Ministry of Health. In the TRAIN 2 study, pCR rates were 68% vs 67% in regimen-containing and non-containing anthracycline, while they were 70% vs 71.4% in our study.[12]

Chemotherapy regimens containing and without anthracycline did not differ significantly in pCR in subgroup analyses, and considering that hematological and non-hematological toxicities are more common in anthracycline containing regimens, it is thought that anthracycline-free chemotherapy as neoadjuvant therapy would be an appropriate option.

In the metaanalysis performed by Ding and his colleagues, 7 randomized controlled trials were evaluated and patients who took and did not take anthracycline in early stage breast cancer were evaluated. As a result of metaanalysis, it has been suggested that opting for an anthracycline-free regimen leads to noninferior consequences. As expected, neutropenia and neutropenic fever were more common in patients who received an anthracycline-containing regimen. In addition, nonhematological side effects such as mucositis, nausea and vomiting were also detected more in the group containing anthracycline. [13]

Conclusions

One of the limitations of our study is that the number of patients is small. One of the reasons for this is that the use of neoadjuvant pertuzumab in our country can still be done with non-indication application approval. Another important limitation is that only cardiotoxicity is evaluated in the side effect profile. However, the main purpose of our study was to show the effect of adding anthracycline regimen to pathological complete response and cardiotoxicity potential in those who used pertuzumab-trastuzumab during the neoadjuvant period.

As a result of the data we obtained, it was concluded that adding anthracycline regimen regimen to dual HER-2 blockade in the neoadjuvant period, regardless of subgroups such as age, stage, menopause status, lymph node positivity, hormone receptor positivity, did not bring additional benefits. In this regard, it is necessary to support our data with studies carried out with larger patient numbers.

Declarations

Funding: None

ETHICAL APPROVAL: Approval was obtained from the Medical Research Ethics Committee of the Manisa Celal Bayar University Faculty of Medicine with the number 99 dated 24.08.2020

PATIENTS' CONSENT: Since the study was a retrospective archive search, informed consent was not obtained from the patients.

CONFLICT OF INTEREST: The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION: A.O, A.P.E., F.E., K.K. and E.A collected the patients data, A.O. and B.K. had done the statistical analysis and wrote the main manuscript text. All authors reviewed the manuscript.

DATA AVAILABILITY STATEMENT: The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Corresponding author Ahmet OZVEREN

Mail address: ahmet_ozveren@yahoo.com phone number:+905533963550

Address: Izmir Private Kent Hospital, Internal Medicine, Medical Oncology Department, Izmir /TURKEY

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