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Research Article

Chemotherapy Choice in Neoadjuvant Dual Her2 Blockade: Is it Really Essential to Add Anthracycline?

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Abstract

Objectives: Addition of trastuzumab and pertuzumab to neoadjuvant chemotherapy in Human epidermal growth factor receptor 2 (HER-2) positive breast cancer is the current clinical standard. We aimed to determine whether anthracycline-containing neoadjuvant chemotherapy yields beneficial effects alongside dual HER-2 blockade, and to assess cardiotoxicity with this treatment.

Methods: Fifty-two patients with HER-2-positive breast cancer who received neoadjuvant chemotherapy were retrospectively evaluated at three tertiary health-care centers. The effects of chemotherapy regimen and several other factors such as age, stage, menopause status, lymph node positivity, and hormone receptor positivity on pathological complete response (pCR) were evaluated.

Results: The mean age at diagnosis was 46±9 years. The pCR rate was similar between those with and without anthracycline-containing regimens (71.4% vs. 70%). Subgroup analyses also showed similar pCR values for those with negative and positive hormone receptors (64.7% vs. 74.3%), those with Ki67 levels <20% and >20% (60% vs. 73.8%), and when premenopausal patients were compared with postmenopausal patients (76.9% vs. 65.4%).

Conclusion: It appears that adding anthracycline to dual HER-2 blockade for neoadjuvant therapy did not yield additional benefits in terms of pCR. Further studies are needed to assess anthracycline-containing regimens in patients who will use the neoadjuvant pertuzumab-trastuzumab combination.

Keywords: Anthracycline, cardiotoxicity, chemotherapy, neoadjuvant chemotherapy, pertuzumab, trastuzumab

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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 an aggressive course and poor prognosis.[2] Dual HER-2 blockade has proven benefits when utilized in metastatic HER-2 positive disease and in the neoadjuvant stage.[3-5]

The main purpose of neoadjuvant therapy is to increase breast protection rates by reducing tumor size.[6] In studies concerning neoadjuvant chemotherapy, the most important primary endpoint is often the rate of pathological complete response (pCR) which is an outcome that is demonstrated to be a determinant of prognosis[7] and has been associated with prolonged survival.[8] In this context, dual HER-2 blockade appears to be advantageous due to

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studies showing increased rates of pCR with this management approach.[9] At present, the clinical standard of care is to add trastuzumab and pertuzumab to neoadjuvant chemotherapy in patients with HER2 positive clinical T2 and/or clinical axillary positive lymph nodes.[10] In the BERENICE study, dual HER-2 blockade with neoadjuvant chemotherapy resulted in pCR rates of up to 75% in patients with HER-2 positivity.[3] Anthracyclines and taxanes are chemotherapeutic agents commonly used in a sequential regimen in the adjuvant and neoadjuvant treatment of early breast cancer to reduce the risk of cancer recurrence. Standard practice is to administer a taxane following anthracycline-based chemotherapy. A high PCR is expected in patients using a dual her2-agent regimen. Is it really necessary to continue using anthracyclines that increase the risk of cardiotoxicity in these patients?

Our aims were to answer the following questions: Does the inclusion of anthracycline have an additional benefit alongside dual HER-2 blockade? Does cardiotoxicity increase with dual HER-2 blockade after anthracycline administration? To answer these questions, we retrospectively evaluated patients who received dual HER-2 blockade in neoadjuvant therapy (according to chemotherapy regimens) and their responses to treatment.

Methods

Ethical approval for this retrospective cohort was received from the Medical Research Ethics Committee of Manisa Celal Bayar University, Faculty of Medicine (approval code: 99, dated August 24, 2020). The clinical characteristics, chemotherapy regimens, laboratory data, pCR rates, and echocardiography results of 52 patients who received pertuzumab and trastuzumab dual HER-2 blockade for neoadjuvant therapy within the prior 3 years were included from three centers: Izmir City Hospital, Manisa Celal Bayar University, Ege University.

The files of the patients included in the study were evaluated in terms of the following parameters; chronic diseases, Eastern Cooperative Oncology Group (ECOG) performance status, tumor multifocality, tumor category (T) lymph node involvement (N) according to TNM classification, histological grade, surgical method, and presence of cardiotoxicity.

Cardiotoxicity defined as a >10% decline in LV ejection fraction (LVEF) from baseline and a final LVEF of <50%.

In the immunohistochemistry (IHC) analysis, those with estrogen receptor (ER) or progesterone receptor (PR) positivity were classified as hormone receptor positive. Tumors with ER and PR negativity were classified as hormone receptor negative. Those with +3 on HER-2 IHC analysis and those who had tested positive for HER-2 fluorescence in situ hybridization were considered to have HER-2 positivity. Ki67 levels in the pretreatment biopsy were also examined and noted. Finally, pathologic CR defined as no residual invasive cancer in the breast and axillary nodes with presence or absence of in situ cancer (ypT0/is ypN0 or ypT0 ypN0). Clinical and pathological staging of patients had been performed according to the American Joint Committee of Cancer classification.[11] All the pathological examinations were performed in Private Izmir Kent Hospital pathology laboratory.

Evaluation of patient files demonstrated that two different chemotherapy regimens had been administered to the 52 patients during their respective neoadjuvant therapies. The first regimen was: Dose-dense adriamycin cyclophosphamide followed by weekly paclitaxel with trastuzumab and pertuzumab. In these patients, anthracycline 60 mg/m2 and cyclophosphamide 600 mg/m^2 were applied once in every 14 days for 4 cycles, then paclitaxel 80 mg/m^2 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 every 21 days. The second chemotherapy regimen was: Docetaxel-carboplatin-trastuzumab-pertuzumab (TCHP). In which, docetaxel 75 mg/m^2, 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) were used-all were administered once every 21 days. Within the scope of the Health Application Reimbursement Scheme of the Turkish Ministry of Health, pertuzumab was used for only four cycles in both regimens.

Statistical Analysis

Factors that may affect pCR (such as age, menopausal condition, clinical stage, histological grade, hormone receptor status, and chemotherapy regimen) were examined by univariate logistic regression models. Odds ratios for all potential predictors were evaluated with a 95% confidence interval. The presence/absence of pCR response was evaluated. In multiple analyses, p values below 0.05 were considered to demonstrate statistical significance. The SPSS version 21 software was used for statistical analysis.

Results

The demographics and laboratory data of the patients at admission are shown in Table 1. The mean age at diagnosis of the 52 patients included in the study was 46±9 (range: 26–67) years.

Table 2 shows distributions according to chronic illness, ECOG performance status, tumor multifocality, tumor cat-

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

	Minimum	Maximum	Mean	Standard 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

egory (T), lymph node involvement, tumor stage, surgical method, histological grade, and side effect of cardiotoxicity.

While 80.8% (n=42) of the patients received anthracycline, 19.2% (n=10) received TCHP regimen 50% of the patients (n=26) were premenopausal at diagnosis, 84.6% (n=44) had Stage 3 tumors, 15.4% (n=8) had Stage 1 or 2 tumors. Hormone receptors were negative in 32.7% (n=17) of the patients. In 80.8% (42) of the patients, Ki67 was over 20%.

The overall pCR rate was 71.2% (n=37) and pCR was 71.4% (n=30) in anthracycline recipients, while it was 70% (n=7) in those who received the TCHP regimen (p=1.000). In patients with breast cancer who received dual HER-2 blockade, it was found that using a regimen containing anthracycline in addition to neoadjuvant therapy did not affect pCR (Table 3).

pCR was significantly higher in those younger than 40 years of age (93.8% vs. 61.1%, p=0.021). According to the TNM classification, the pCR was 94.7% in those with N1 and 57.6% in those with N2-3 (p=0.004) (Table 3). In terms of regimen, 68.4% of those in the N1 group received an anthracycline containing regimen, while 87.9% of the N2-3 group received a regimen containing anthracycline (p=0.142).

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

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
Localization 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
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

disease. The difference was not significant (p=0.412). In those with Stage 3 disease, regimens containing anthracyclines were administered to 81.8% of patients, while 75% of patients in the Stage 1–2 group received anthracyclines (p=0.642).

Hormone receptor positivity or Ki67 above 20% did not significantly affect the pCR.

Cardiotoxicity was detected in 5.8% (n=3) of patients with dual blockade. All of these individuals were younger than

Table 3. Pathological response status in relation to several variables

	Count (% in column)	Pathological response		p
		Presence of Residuals (% in row)	pCR (% in row)	
Chemotherapy regimen				1.000
Anthracycline	42 (80.80)	12 (28.6)	30 (71.4)	
Platinum-based	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
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)	

65 years of age and had received anthracycline-containing regimen as well as dual HER-2 blockade. HER-2 blockade was terminated in these patients as soon as cardiotoxicity was detected.

Discussion

In HER-2(+) Stage 4 breast cancer, higher pCR rates have been reported with the use of double HER-2 blockade during neoadjuvant therapy.[3, 4] Achieving pCR after neoadjuvant treatment has been shown to be a positive prognostic factor.[11, 12] In the BERENICE study, high pCR rates were obtained with anthracycline-containing regimens in patients with HER2 positivity who had received dual HER2 blockade. Such findings have necessitated the evaluation of the additional advantages and possible side effects of anthracycline-containing regimens.[3]

In the TRAIN 2 study, there was no significant difference regimens with and without anthracycline, and it was reported that it was preferable to not use anthracyclines.[13] The pCR rate obtained in our study was found to be similar in the two regimens with and without anthracycline. All patients with cardiotoxicity (5.8%) were those who had received the treatment regimen containing anthracyclines. The anthracycline-containing regimen used in the TRAIN 2 study was different from the one preferred in our study. In addition, in the TRAIN 2 study, patients received nine cycles of HER2 dual blockade; whereas, in our study, this was limited to four cycles in accordance with the restrictions imposed by the Turkish Ministry of Health. In the TRAIN 2 study, pCR rates were 68% vs. 67% in anthracycline-containing and non-anthracycline regimens, respectively.[14] In the present study, pCR rates were 70% vs. 71.4%.

Chemotherapy regimens with and without anthracycline did not differ significantly in terms of pCR outcomes, and similar findings were observed in subgroup analyses. Considering that hematological and non-hematological toxicities are more common with anthracycline-containing regimens, it is feasible to suggest that anthracycline-free

chemotherapy may be a preferred for neoadjuvant therapy.

In the meta-analysis performed by Ding and colleagues, seven randomized and controlled trials were evaluated and patients who did or did not receive anthracyclines in early stage breast cancer were evaluated. As a result of the meta-analysis, it has been suggested that opting for an anthracycline-free regimen leads to non-inferior outcomes. As expected, neutropenia and neutropenic fever were more common in patients who received an anthracycline-containing regimen. In a phase-2 study in which neoadjuvant dual anti-HER2 blockade was not used, the non-anthracycline TCH regimen was superior to the anthracycline-containing regimen.[15] Considering that dual anti-HER2 therapy results in higher response rates, it becomes clear that anthracyclines do not need to be used in every patient. In addition, non-hematological side effects such as mucositis, nausea, and vomiting were also detected in anthracycline recipients.[13] Since we did not evaluate side effects other than cardiotoxicity in our study, we did not look for changes in the frequency of neutropenia and neutropenic fever between the groups.

The retrospective design of our study and the small number of patients were our major limitations. One of the reasons for this is that the use of neoadjuvant pertuzumab in our country can be administered only after receiving approval with an application for "non-indication use." Another important limitation is that only cardiotoxicity was evaluated in the side effect profile. However, the main purpose of our study was to show the effect of adding anthracycline regimen on pCR and to assess cardiotoxicity potential in those who used pertuzumab-trastuzumab during the neoadjuvant period. In our study, we could not evaluate the side effects other than cardiotoxicity because the side effects were not adequately graded in the file system. This is another limitation of our study.

Conclusion

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

Disclosures

Ethics Committee Approval: Approval was obtained from the Medical Research Ethics Committee of the Manisa Celal Bayar University Faculty of Medicine with the number 99 dated August 24, 2020.

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References

1. Ross JS, Fletcher JA. The HER-2/neu oncogene: prognostic factor, predictive factor and target for therapy. Semin Cancer Biol 1999;9:125–38.
2. Ross JS, Slodkowska EA, Symmans WF, Pusztai L, Ravdin PM, Hortobagyi GN. The HER-2 receptor and breast cancer: ten years of targeted anti-HER-2 therapy and personalized medicine. Oncologist 2009;14:320–68.
3. Swain SM, Ewer MS, Viale G, Delaloge S, Ferrero JM, Verrill M, et al; BERENICE Study Group. Pertuzumab, trastuzumab, and standard anthracycline- and taxane-based chemotherapy for the neoadjuvant treatment of patients with HER2-positive localized breast cancer (BERENICE): a phase II, open-label, multicenter, multinational cardiac safety study. Ann Oncol 2018;29:646–53.
4. Tiwari SR, Mishra P, Raska P, Calhoun B, Abraham J, Moore H, et al. Retrospective study of the efficacy and safety of neoadjuvant docetaxel, carboplatin, trastuzumab/pertuzumab (TCH-P) in nonmetastatic HER2-positive breast cancer. Breast Cancer Res Treat 2016;158:189–93.
5. Baselga J, Swain SM. CLEOPATRA: a phase III evaluation of pertuzumab and trastuzumab for HER2-positive metastatic breast cancer. Clin Breast Cancer 2010;10:489–91.
6. Chen AM, Meric-Bernstam F, Hunt KK, Thames HD, Oswald MJ, Outlaw ED, et al. Breast conservation after neoadjuvant chemotherapy: the MD Anderson cancer center experience. J Clin Oncol 2004;22:2303–12.
7. Prowell TM, Pazdur R. Pathological complete response and accelerated drug approval in early breast cancer. N Engl J Med 2012;366:2438–41.
8. Symmans WF, Wei C, Gould R, Yu X, Zhang Y, Liu M, et al. Long-term prognostic risk after neoadjuvant chemotherapy associated with residual cancer burden and breast cancer subtype. J Clin Oncol 2017;35:1049.
9. Schneeweiss A, Chia S, Hickish T, Harvey V, Eniu A, Hegg R, et al. Pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer: a randomized phase II cardiac safety study (TRYPHAENA). Ann Oncol 2013;24:2278–84.
10. Gradishar WJ, Moran MS, Abraham J, Aft R, Agnese D, Allison KH, et al. Breast cancer, version 3.2022, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 2022;20:691–722.

11. Houssami N, Macaskill P, von Minckwitz G, Marinovich ML, Mamounas E. Meta-analysis of the association of breast cancer subtype and pathologic complete response to neoadjuvant chemotherapy. Eur J Cancer 2012;48:3342–54.
12. Chollet P, Amat S, Cure H, De Latour M, Le Bouedec G, Mouret-Reynier M, et al. Prognostic significance of a complete pathological response after induction chemotherapy in operable breast cancer. Br J Cancer 2002;86:1041–6.
13. Ding W, Li Z, Wang C, Dai J, Ruan G, Tu C. Anthracycline versus nonanthracycline adjuvant therapy for early breast cancer: A systematic review and meta-analysis. Medicine (Baltimore) 2018;97:e12908.
14. van Ramshorst MS, van der Voort A, van Werkhoven ED, Mandjes IA, Kemper I, Dezentjé VO, et al. Neoadjuvant chemotherapy with or without anthracyclines in the presence of dual HER2 blockade for HER2-positive breast cancer (TRAIN-2): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol 2018;19:1630–40.
15. Gao HF, Wu Z, Lin Y, Song XY, Cao Y, Chen QJ, et al. Anthracycline-containing versus carboplatin-containing neoadjuvant chemotherapy in combination with trastuzumab for HER2-positive breast cancer: the neoCARH phase II randomized clinical trial. Ther Adv Med Oncol 2021;13:17588359211009003.