RESEARCH ARTICLE / *Araştırma Makalesi*

Pertuzumab-Mediated Cardiotoxicity: A Single Center Study

Pertuzumab Aracılı Kardiyotoksisite: Tek Merkezli Bir Çalışma

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Abstract

Introduction	Recent clinical trials have shown that adding pertuzumab to trastuzumab improved the cellular response to therapy and provides a survival benefit compared with trastuzumab alone. However, it has raised concerns about additive risk of cardiotoxicity. Real life data on pertuzumab-induced cardiotoxicity are limited.
Materials and Methods	Patients a diagnosis of breast cancer who had been treated trastuzumab plus pertuzumab between January 2017 and June 2022 and had undergone regularly transthoracic echocardiography, as a part of control visits, in our medical center were included. We performed descriptive statistical analysis to evaluate the patients' characteristics and therapies, which could increase the risk of cardiac adverse events. Cardiotoxicity was evaluated by serial left ventricular ejection fraction (LVEF) measuring by 2D echocardiography at baseline and every three months during pertuzumab therapy and was defined as a decrease in LVEF > 10% to below 55%.
Results	There were 118 patients fulfilling the inclusion criteria. The median age of the population was 51 (41-60) years. The median duration of pertuzumab therapy was 15 (9–57) weeks. Pertuzumab therapy was discontinued in two patients because of an allergic reaction and in other two patients due to cardiotoxicity. The reduced LVEF did not recover to baseline values in either patient.
Conclusion	The incidence of cardiotoxicity (1.69%) in the current study was no higher than expected for trastuzumab alone. Data from previous studies and the results of this study support that pertuzumab causes no increase in cardiotoxicity. Still, large clinical trials are needed to verify the cardiac safety of pertuzumab in a real-world setting.
Keywords	breast cancer; cardiotoxicity; pertuzumab.

Öz

Amaç	*Son klinik çalışmalar, trastuzumaba pertuzumab eklenmesinin tedaviye hücresel yanıtı iyileştirdiğini ve tek başına trastuzumab ile karşılaştırıldığında sağkalım avantajı sağladığını göstermiştir. Bununla birlikte, kardiyotoksisite riskini arttırabileceği konusunda endişe uyandırmıştır. Pertuzumabın neden olduğu kardiyotoksisiteye ilişkin gerçek yaşam verileri kısıtlıdır.*
Yöntem ve Gereçler	*Ocak 2017-Haziran 2022 tarihleri arasında trastuzumab beraberinde pertuzumab tedavisi gören ve kontrol vizitleri kapsamında düzenli olarak transtorasik ekokardiyografi çekilen hastalar çalışmaya dahil edildi. Kardiyak advers olay riskini arttırabilecek hasta özelliklerini ve tedavilerini değerlendirmek için tanımlayıcı istatistiksel analizler kullanıldı. Başlangıçta ve pertuzumab tedavisi sırasında her 3 ayda bir 2 boyutlu ekokardiyografi ile yapılan ardışık sol ventrikül ejeksiyon fraksiyonu (SVEF) ölçümleri değerlendirildi ve SVEF'nin %10'dan fazla düşüşle %55'in altına inmesi kardiyotoksisite olarak tanımlandı.*
Bulgular	*Dahil edilme kriterlerini karşılayan 118 hasta vardı. Populasyonun yaş ortancası 51 (41-60) yıldı. Pertuzumab tedavisinin ortanca süresi 15 (9-57) haftaydı. Pertuzumab tedavisi iki hastada alerjik reaksiyon, diğer iki hastada kardiyotoksisite nedeniyle kesildi. Azalan SVEF her 2 hastada da başlangıç değerlerine geri dönmedi.*
Sonuç	*Mevcut çalışmada kardiyotoksisite insidansı (%1,69) tek başına trastuzumab için beklenenden daha yüksek değildi. Önceki çalışmalardan elde edilen veriler ve bu çalışmanın sonuçları pertuzumabın kardiyotoksisitede artışa neden olmadığını desteklemektedir. Yine de, gerçek yaşam koşullarında pertuzumabın kardiyak güvenliliğini desteklemek için büyük çaplı klinik çalışmalara ihtiyaç vardır.*
Anahtar Kelimeler	*meme kanseri; kardiyotoksisite; pertuzumab.*

INTRODUCTION

Human epidermal growth factor receptor 2 (HER2) positive breast cancer comprises nearly 20% of the breast cancer cases.[1] Before, it was a poor prognostic feature to have HER2-positive breast cancer, but with the introduction of anti-HER2 agents prognosis changed dramatically and survival increased in this patient group.[2-4] Recent studies have provided new proof about the positive effects on treatment response and survival benefit of the pertuzumab in addition to trastuzumab.[5-6] Pertuzumab binds to an epitope on the HER2 receptor different from trastuzumab and displayed synergistic effects on the antitumor activity with trastuzumab.[7]

Pertuzumab is administered with trastuzumab and usually along with taxanes according to the chemotherapy regimens.[8,9] Before patients with HER2 positive breast cancer had approximately 20.3 months of survival under trastuzumab therapy, median survival time increased to 48 months with administration of trastuzumab, pertuzumab, docetaxel combination.[10,11]

While the prognosis of breast cancer improves and survival prolonged, it brings together increased concerns about drug-related adverse events.[12] While trastuzumab-related cardiac dysfunction is well documented, pertuzumab-related cardiac adverse events are less established.

Current data about the cardiac effects of pertuzumab are conflicting. The Neosphere trial reported a mild increase in left ventricular ejection fraction (LVEF) decline with pertuzumab combination compared with the control group, some trials showed no increase in the incidence of drug-related cardiotoxicity in case of addition pertuzumab to trastuzumab.[6,13,14]

Current evidence about the cardiotoxicity potential of pertuzumab usually comes from phase 2 and phase 3 clinical trials and real life data may differ from these results. However, there is a possibility that the possible selection bias prefers healthier or younger persons to enroll in clinical trials. There is limited data about the cardiac outcomes of breast cancer patients under pertuzumab therapy in real-life settings. Therefore, we evaluated the pertuzumab-related cardiotoxicity in patients with breast cancer following at a tertiary care center oncology clinic.

MATERIALS and METHODS

The data of the patients with a diagnosis of HER2-positive breast cancer and who had been treated with pertuzumab in a tertiary care center were recorded. Patients who came for follow-up visits also underwent echocardiographic examinations regularly enrolled in the study. Subjects with baseline LVEF ≥55% were included and patients with irregular control visits or absent echocardiographic examinations were excluded.

In this retrospective observational study, baseline clinical characteristics, comorbidities, previous chemotherapeutic agents, mastectomy or left-sided radiotherapy history, current drugs, smoking status, echocardiography results, duration of pertuzumab therapy, the stage of the disease were analyzed.

Asymptomatic EF drop, congestive heart failure clinic, cardiac ischemic symptoms or signs of cardiac arrhythmia was accepted as cardiac adverse events. Follow-up echocardiographic examinations during pertuzumab therapy were comparatively evaluated. A reduction in LVEF > 10% to below 55% between pre- and post-pertuzumab echocardiography was defined as cardiotoxicity.

There was no definitive echocardiography schedule to follow-up pertuzumab cardiotoxicity. It was suggested to perform echocardiographic examinations for 3,6,9,12 months in the adjuvant therapy. In metastatic disease, patient should undergo echocardiography at baseline and then first 3–12 months of therapy and then if the patient complains of cardiac symptoms.[15]

The measurements of wall thickness, left atrial and left ventricular diameters were performed at baseline and follow-up examinations. Left ventricular EF was calculated using a modified Simpson method using 2D echocardiographic images (Philips Epiq 7 ultrasound systems; Bothel, WA, USA). Valvular disorders were also recorded. The cardiac symptoms of heart failure, coronary ischemia, or arrhythmia had been questioned during follow-up visits in the oncology clinic and each patient had undergone echocardiography before every pertuzumab cycle and if a new cardiac symptom was presented. Medical records containing these issues were screened.

The ethic approval was obtained from the local ethics committee and the current study was conducted according to with the Declaration of Helsinki.

Statistical analyses

Statistical analyses were performed using SPSS version 22 (SPSS Inc.,Chicago, IL,USA). Descriptive statistics were used to define the clinical characteristics of the population, which may have a potential effect about cardiotoxicity.

Categorical variables were expressed as counts and percentage, whereas continuous variables with a normal distribution were presented as mean ± standard deviation and continuous variables with abnormal distribution were expressed as median (interquartile range) or median (25th-75th percentile) after examining with Kolmogorov-Smirnov test. Continuous echocardiographic variables with abnormal distribution were compared with Wilcoxon test before and after chemotherapy.

A p value under 0.05 was set as statistically significant for all analysis.

RESULTS

A total of 118 patients who met the inclusion criteria were included in the study, only one (0.84%) of them were male. The median age of the population was 51 (41-60) years and the age of the patients varied between 27 and 82 years old. The mean duration of the pertuzumab therapy was 15 (9–57) weeks.

One had coronary artery disease and none of them had heart failure on admission. One hundred sixteen (98.30%) patients had received concomitantly or previously taxanes whereas 70 (59.32%) patients had been given anthracycline earlier. The other clinical characteristics are listed in Table 1.

Table 1: Clinical characteristics of the study population.

Variables	**n (%)**
Stage of the Breast Cancer	
-Stage 2	2 (1.7%)
-Stage 3	60 (50.8%)
-Stage 4	56 (47.5%)
Previous therapies	
-Anthracycline	70(59.3%)
-Cyclophosphamide	63 (53.4%)
-5 fluorouracil	15 (12.7%)
-Tamoxifen	10 (8.5%)
-Vinca alkaloids	9 (7.6%)
Left-sided radiotherapy	15 (12.7%)
Mastectomy	31 (26.3%)
Hypertension	17 (14.4%)
Diabetes mellitus	11 (9.3%)
Chronic kidney disease	3 (2.5%)
Current drugs	
-Beta blockers	3 (2.5%)
-ACE inhibitors/ARBs	11 (9.3%)
Smoking status	
-Never	85 (72%)
-Active or ex-smoker	22 (18.6%)
-Unknown	11 (9.3%)

The prevalence is given as count (n) and percentages (%).
ACE: Angiotensine converting enzyme, ARBs: Angiotensin receptor blockers

Echocardiographic examinations showed no significant difference before and after chemotherapy. (Table 2) Median LVEF was 60% (58%-64%) at baseline, 60% (58%-63%)

at third month and 61% (60%-63%) at twelfth month. The LVEF difference was not significant between baseline and third month (p=0.419) or between baseline and twelfth month (p=0.447). Fiftyfive patients (46.6%) had mild mitral regurgitation and two patients (1.6%) had moderate mitral regurgitation. Seven patients (5.9%) had mild aortic regurgitation and two patients (1.6%) had moderate aortic regurgitation whereas four patients (3.3%) had mild aortic stenosis. No progression of valvular diseases was observed during study period.

Table 2: Comparison of echocardiographic measurement between baseline and twelfth month.

Variables	Baseline	12th Month	P value
Interventricular septum thickness	1 (0.9-1.1)	1 (0.9-1.1)	0.271
Posterior wall thickness	1 (0.9-1.1)	1 (0.9-1.1)	0.412
Left atrial diameter	3.3 (3.2-3.6)	3.4 (3.2-3.6)	0.156
Left ventricular diameter	4.2 (4-4.5)	4.3 (4-4.5)	0.056

The values were given as median (25th-75th percentile).
P value<0.05 was considered statistically significant.

None of the patients experienced symptoms or signs of cardiac arrhythmia or coronary ischemia. Left ventricular EF decline occurred in only two patients. In the case of pertuzumab-related cardiomyopathy first the drug should be interrupted and then treatment for the LVEF drop should be initiated.

Pertuzumab therapy was cessassed in four patients. The reason in two patients was an allergic reaction to pertuzumab. The other two patients experienced drug-related cardiotoxicity.

One of them was 53 years old with stage 3 breast cancer. She had never smoked before. She had no history of hypertension, diabetes mellitus or left-sided radiotherapy. She had received anthracycline and cyclophosphamide earlier. Alone trastuzumab had been administered before pertuzumab trastuzumab docetaxel combination. Her LVEF decreased to 45% from 62% after the second cycle of pertuzumab and trastuzumab therapy and she presented with New York Heart Association (NYHA) class 2 heart failure symptoms. After discontinuation of trastuzumab and pertuzumab, candesartan and carvedilol were initiated. Nevertheless, her LVEF did not increase during 78 weeks follow-up period.

The other patient was 40 years old with stage 3 breast cancer. A reduction in LVEF from 65% to 30% was detected after the third cycle of pertuzumab and trastuzumab combination. She experienced NYHA class 1 heart failure symptoms. Two drugs stopped immediately and ramipril and metoprolol were prescribed. She had no history of smoking, hypertension, diabetes mellitus or left-sided radiotherapy. She had been previously treated with antracycline and cyclophosphamide. Unfortunately, an increase in LVEF was not detected during 8 weeks of control echocardiographic examinations yet.

Due to low incidence of cardiotoxicity, further statistical analyses cannot be performed to search for the association between drug-related cardiotoxicity and possible risk factors.

DISCUSSION

Pertuzumab related LVEF decline occurred in only two (1.69%) patients. This result is consistent with previous studies, which reported low-discontinuation rate related to pertuzumab associated cardiotoxicity. Unfortunately, LVEF of both patients did not return to normal levels in spite of standard-heart failure therapy. Left atrial and left ventricular diameters did not displayed significant difference before and after pertuzumab therapy. This was not surprising because atrial or ventricular enlargements were expected usually in case of heart failure and the incidence of drug related heart failure was very low in the study population. In parallel with our findings, we also did not find any literature data reporting change in ventricular wall thickness or valvular heart disease progression after pertuzumab administration.

Despite the beneficial effects, there are concerns about the cardiotoxicity of dual anti-HER2 therapy. Blockage of the HER2 cascade at two different points may lead to an increased risk of cardiotoxicity. Because HER2 pathway plays an important role in growth and repair signaling of the cardiomyocytes.[16] However, previous clinical trials support the cardiac safety of trastuzumab plus pertuzumab therapy not only along with taxanes but also given after anthracycline drugs.[5,17,18] Current clinical trials researching pertuzumab reported the rate of cardiac adverse events can vary between 4.5%-14.5%.[19]

Lenihan et al. evaluated 598 patients receiving pertuzumab and reported 35 (5.9%) patients experienced asymptomatic LVEF drop and 4 (0.7%) patients presented with symptomatic heart failure.[20] Cardiotoxicity incidence was as low as aforementioned in our study population (1.6%). The CLEOPATRA trial reported a cardiac event rate of 16.4% in the placebo group and 14.5% in the pertuzumab group, which consisted of patients with metastatic breast cancer.[18] Decline of any grade in LVEF was detected in 8.3% of placebo patients and in 4.4% of pertuzumab patients. Congestive heart failure clinic was detected in only 1.8% of the placebo arm and 1.0% of the pertuzumab arm. This is the point of care, previous anthracycline therapy and radiotherapy exposure increase the risk of cardiotoxicity. In our study population because of low count of patients with cardiotoxicity, this hypothesis cannot be examined. The two patients with cardiotoxicity had given anthracycline but had not received left-sided radiotherapy. The NeoSphre and TRYPHAENA trials, which researching pertuzumab therapy in neoadjuvant settings also reported low rate of cardiac adverse events.[5,6]

However, in a meta-analysis eight randomized controlled trials investigating pertuzumab (consist of 8420 patients) were included and it was concluded while patients under pertuzumab therapy were at increased risk of clinical heart failure compared with placebo, there was no rise in the incidence of asymptomatic or mildly symptomatic LVEF reduction with pertuzumab.[21] Patients had received anthracycline concomitantly or previously in six of these eight studies. The median pertuzumab therapy duration was 18 (1–65) cycles. The pooled incidence of asymptomatic or mildly symptomatic LV systolic dysfunction was 3.5% in the pertuzumab arm and 3.1% in the placebo arm. (Risk ratio [RR]: 1.19, 95% CI:0.89–1.61). It was also reported that patients under pertuzumab therapy had two fold-increased risk of clinical symptomatic heart failure compared with placebo. (RR:1.97; 95% CI: 1.05–3.70) These results are partially conflicting with previous studies that had reported cardiac safety of pertuzumab use either in alone or along with other anti-HER2 agents.[18-20,22]

This is the point of care the above-discussed data belong to phase 2 or 3 clinical trials and it was speculated that the incidence of cardiac side effects of chemoterapeutic agents may be higher than in clinical studies, because of the older age group or patients with cardiovascular risk factors in daily practice.

The current study had several limitations. First, due to low count of patients who experienced drug related cardiomyopathy with pertuzumab, it was impossible to characterize the cardiac adverse effects profile of this agent. Second, this study was retrospective and so dependent on medical records. Moreover, it would be better to use also tissue Doppler or strain echocardiography to evaluate the cardiac toxicity of pertuzumab, which are expected to detect early or subclinical cardiac damages. The last limitation was absence of coronary artery angiography to eliminate definitely ischemic etiologies in patients with decreased EF.

CONCLUSION

The current data support that pertuzumab combination with trastuzumab has a low risk of cardiotoxicity. Cumulating evidence on the cardiac safety of dual anti-HER2 treatment will encourage the clinicians to use this combination in daily practice whenever indicated. Real life data with longer follow-up period is needed to better under-

stand the cardiac effects of pertuzumab.

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Conflicts of interest

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Author contributions

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This study was approved by Baskent University Institutional Review Board and Ethics Committee (Date: 23/06/2020 Project no: KA20/255)

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