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# Treatment Outcomes of HER-2 Positive Metastatic Breast Cancer Patients Treated with Pertuzumab in the First Line Setting- Real Life Experience

## Birinci Basamakta Pertuzumab ile Tedavi Edilen Her-2 Pozitif Metastatik Meme Kanserli Hastaların Sonuçları: Gerçek Yaşam Verisi

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**ABSTRACT**

**Objective:** Pertuzumab, a new recombinant humanized monoclonal antibody, has been developed to inhibit the formation of HER2:HER3 heterodimerization. The clinical benefit of pertuzumab therapy in HER2 positive metastatic Breast Cancer (mBC) patients in the first-line setting has been shown in previous phase III studies. Herein we aimed to analyze the efficacy and toxicity profile of pertuzumab in patients with HER2 positive mBC.
**Materials and Methods:** This was a retrospective study of 28 patients with mBC followed from two different centers in Turkey. All patients were treated with pertuzumab in the first line setting, with a combination including trastuzumab and docetaxel. Treatment outcomes along with drug efficacy and safety were retrospectively analyzed.
**Results:** At a median follow-up time of 10.1 (2.4-25.2) months, among the 28 patients, 1 (3.6%) case of death and 2 (7.1%) cases of progression occurred. The median age was determined as 47 (18-74) years. Excluding 1 patient, all had (96.4%) de-novo metastatic disease at presentation. The median number of treatment cycles was 7 (4 - 12) for docetaxel, 18 (4 - 35) for pertuzumab + trastuzumab, and 10 (1 - 29) for the maintenance therapy (pertuzumab + trastuzumab). The most common side effects were fatigue (75%) and arthralgia/myalgia (64.3%). Grade 3 or 4 toxicity was observed to be very infrequent as follows: neutropenia; grade 3 in 4 (14%) patients and grade 4 in 1 (3.6%) patient, neuropathy; grade 3 in 5 (17.8%) patients.
**Conclusion:** Even with a small sample size, our results confirm that pertuzumab + trastuzumab + docetaxel combination therapy in the first line setting for HER2 positive mBC patients is the standard of care, with acceptable toxicity profile.

**Key Words:** Metastatic breast cancer, HER2 positive, pertuzumab, progression free survival, overall survival, toxicity

**ÖZET**

**Amaç:** Pertuzumab HER2:HER3 heterodimerizasyon oluşumunu inhibe eden, yeni geliştirilen bir rekombinant humanize monoklonal antikordur. Daha önce yapılan faz III çalışmalarda, HER2 pozitif metastatik Meme Kanseri (mMK) hastalarında pertuzumabın klinik faydası gösterilmiştir. Biz de bu çalışmada HER2 pozitif mMK'li hastalarda pertuzumabın etkinlik ve toksisite profilini analiz etmeyi amaçladık.
**Gereç ve Yöntemler:** Çalışmamızda Türkiye'deki iki farklı merkezden takip edilen 28 mMK hastasının retrospektif verileri incelenmiştir. Tüm hastalar birinci basamakta pertuzumab ile tedavi edilmişti. İlaç etkinliği ve güvenliği ile birlikte tedavi sonuçları retrospektif olarak analiz edildi.
**Bulgular:** Ortanca 10.1 (2.4-25.2) ay takip süresince, toplam 28 hastada, 1 (%3.6) ölüm vakası ve 2 (%7.1) progresyon vakası gerçekleşti. Ortanca yaş 47 (18-74) olarak saptandı. Bir hasta hariç, hastaların hepsi (%96.4) de-novo metastatikti. Ortanca kür sayıları; dosetaksel için 7 (4 – 12), pertuzumab + trastuzumab için 18 (4 – 35) ve idame pertuzumab + trastuzumab için 10 (1 – 29) olarak saptandı. En sık görülen yan etkiler; yorgunluk (%75) ve artralji-myaljiydi (%64.3). Grade 3-4 yan etkiler çok nadir görülmekle birlikte; 4 (%14) hastada grade 3 ve 1 (%3.6) hastada grade 4 nötropeni, 5 (%17.8) hastada grade 3 nöropati görüldü.
**Sonuç:** Az sayıda hasta içeren bir grup olsa da, sonuçlarımız pertuzumab + trastuzumab + dosetaksel kombinasyon tedavisinin birinci basamak HER2 pozitif mMK hastalarında kabul edilebilir bir toksisite profiline sahip standart bir tedavi olduğunu desteklemektedir.

**Anahtar Kelimeler:** Metastatik meme kanseri, HER2 pozitif, pertuzumab, progresyonsuz sağkalım, genel sağ kalım, toksisite

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## Introduction

Breast Cancer (BC) is the most common malignancy in women worldwide, with an estimated 1,671,149 cases and 521.907 deaths in 2012 (1). Human Epidermal Growth Factor Receptor-2 (HER2), which was first found out in 1985, is a kind of well-defined transmembrane protein. In 1987, HER-2 amplification was identified in nearly 25% of BC cases, being shown as a negative predictor of worse survival (2). Laboratory findings have shown HER2 amplification as a main contributor to the BC pathogenesis (3, 4). Although HER2-positive BC is associated with poor outcomes, the clinical results have significantly changed with the advent of HER2-targeted treatments (5), the first of which is known as trastuzumab and approved by Food and Drug Administration (FDA) in 1998. Trastuzumab in combination with first-line chemotherapy have resulted in a longer time to disease progression, higher response rate, durable response, and improved Overall Survival (OS) compared to standard chemotherapy alone (6) in early and metastatic HER2-positive disease (7).

Although there are positive and remarkable changes in the treatment of HER2-positive BC patients treated with trastuzumab, recurrence and progression rates are still continuing, with nearly 15% of patients developing distant metastasis within 12 months after treatment completion. However, HER2 oncogene is still an important driver for both tumor development and survival in patients receiving trastuzumab. More recently, new anti-HER2 drugs are being developed in order to overcome HER2 resistance, with multiple ongoing studies investigating their clinical benefits (8). The heterodimerization of HER2 with other known HER transmembrane proteins, especially with HER3, is one of the most important mechanisms for trastuzumab resistance (9). The new recombinant humanized monoclonal antibody pertuzumab has been developed to prevent the formation of HER2:HER3 heterodimers, with the goal of overcoming this resistance mechanism (10), since this formation is responsible for both antibody-dependent cytotoxicity and apoptosis (11). The phase III CLEOPATRA trial was designed in the first-line setting in patients with HER2-positive metastatic BC. Pertuzumab in combination with trastuzumab + docetaxel improves progression free survival (PFS) and OS compared to the trastuzumab + docetaxel combination, hence was approved by FDA in June 2012 for patients with HER2-positive metastatic BC who have not received prior anti-HER2 therapy (12). Herein we performed a multicenter retrospective study to evaluate the efficacy and toxicity profile of pertuzumab in patients with HER2-positive metastatic BC from Turkish population.

## Material and Methods

*Data enrollment:* From March 2016 to August 2018, a total of 28 metastatic BC patients from two centers in Turkey, who were treated with pertuzumab + trastuzumab + docetaxel combination for HER2-positive metastatic disease in the first-line setting, were retrospectively analyzed. Patients with histologically confirmed HER2-positive metastatic BC were included in the study. While HER2 status was accepted as positive in patients with c-erb-B2 score 3(+) by immunohistochemical staining, its status in those with c-erb-B2 score 2(+) was confirmed by silver in situ hybridization or fluorescence in situ hybridization.

**Ethical Approval:** For this study, approval was obtained from Local Ethics Committee, with the decision number 2018/1533. This retrospective study was designed in accordance with the World Medical Association Declaration of Helsinki, "Ethical Principles for Medical Research Involving Human Subjects", amended in October 2013. Since it is a retrospective study, patient consent form could not be obtained.

**Treatment and Design:** This retrospective and multi-center study assessed the efficacy and toxicity profile of pertuzumab in HER2-positive metastatic BC patients who had not received prior anti-HER2 therapy. Baseline data including disease characteristics, demographic features, laboratory parameters, Performance Status (PS), treatments, response to treatments, and toxicities were carefully recorded. Pertuzumab was administered at a loading dose of 840 mg followed by a maintenance dose of 420 mg in combination with docetaxel 75 mg/m² + trastuzumab loading dose of 8mg/kg followed by maintenance dose of 6 mg/kg, with a cycle repeated every 21 days. Docetaxel was given minimum 4 and maximum 12 cycles. The maintenance therapy with pertuzumab + trastuzumab combination was continued until disease progression, unacceptable toxicity, or patient's withdrawal.

**Disease Assessment:** The evaluation of treatment responses was performed every 3 months by computed tomography or PET-CT in accordance with the Response Evaluation Criteria in Solid Tumor (RECIST) version 1.1. National Cancer Institute Common Terminology Criteria of Adverse events (NCI CTCAE) version 4.0 was used to grade the adverse events.

**Table 1.** Patient General Characteristics

| Characteristics | Patients, n=28 (%) |
|---|---|
| Age(year), median (range) | 47 (18-74) |
| Menopausal status, n (%) | |
| Premenopausal | 14 (50.0) |
| Perimenopausal | 2 (7.1) |
| Postmenopausal | 12 (42.9) |
| Histological type, n (%) | |
| IDC | 27 (96.4) |
| ILC | 1 (3.6) |
| De-novo metastatic disease, n (%) | |
| Yes | 27 (96.4) |
| No | 1 (3.6) |
| Hormonal status, n (%) | |
| ER/PR positive | 17 (60.7) |
| ER/PR negative | 6 (21.4) |
| ER+/PR- | 4 (14.3) |
| ER-/PR+ | 1 (3.6) |
| HER2 positivity, n (%) | |
| IHC3+ | 22 (78.6) |
| IHC2+/FISH+ | 6 (21.4) |
| Grade, n (%) | |
| 1 | 1 (3.6) |
| 2 | 12 (42.9) |
| 3 | 9 (32.1) |
| Unknown | 6 (21.4) |
| Ki-67 (%), median (range) | 30 (5-80) |
| Smoking status, n (%) | |
| Yes | 19 (66.9) |
| No | 9 (32.1) |

**IDC**, Invasive Ductal Carcinoma; **ILC**, Invasive Lobular Carcinoma; **ER**, Estrogen receptor; **PR**, Progesterone receptor; **HER2**, Human epidermal growth factor receptor-2.**IHC**, Immunohistochemical

**Statistical Analysis**: The computer program 'Statistical Package for The Social Sciences' version 21.0 for Windows (SPSS, Inc. Chicago, IL, USA) was used for all statistical analysis. For descriptive statistics; categorical variables were presented as frequency distributions and percentages, whereas continuous numerical variables were given as medians, minimum and maximum values. Survival were analyzed using the Kaplan-Meier method and were compared by Log-rank statistics. p value less than 0.05 was considered statistically significant. PFS was defined as the time from the day of pertuzumab initiation to the day of disease progression or death due to any reason. OS was defined as the time from the starting day of pertuzumab to the day of death due to any cause.

## Results

At a median follow-up time of 10.1 (2.4-25.2) months, among the 28 patients, 1 (3.6%) case of death and 2 (7.1%) cases of progression occurred. The median age was 47 (18-74) years. The number of premenopausal, perimenopausal, and postmenopausal patients was 14 (50.0%), 2 (7.1%), and 12 (42.9%), respectively. Excluding 1 patient, all had (96.4%) de-novo metastatic disease at presentation, with 6 (21.4%) of them being hormone receptor-negative BC. Demographic characteristics were given in Table 1. Considering the chemotherapy cycles administered in this analysis, the median number of treatment cycles was 7 (4 - 12) for docetaxel, 18 (4 - 35) for pertuzumab + trastuzumab, and 10 (1 - 29) for the maintenance therapy (pertuzumab + trastuzumab).

**Table 2.** Adverse Events

| | Patients n=28 (%) | Characteristics | Patients n=28 (%) |
|---|---|---|---|
| Follow-up time, month, median (range) | 10.1 (2.4-25.2) | Asthenia | |
| | | No | 17 (60.7) |
| | | Yes | 11 (39.3) |
| Chemotherapy cycle, median (range) | 18 (4-35) | Nausea | |
| | | No | 15 (53.6) |
| | | Yes | 13 (46.4) |
| Docetaxel cycle, median (range) | 7 (4-12) | Nausea grade | |
| | | Grade 1 | 11 (84.6) |
| | | Grade 2 | 2 (15.4) |
| Maintenance therapy cycle, median (range) | 10 (1-29) | Alopecia | |
| | | No | 13 (46.4) |
| | | Yes | 15 (53.6) |
| Dose reduction (Docetaxel) | | Myalgia | |
| Yes | 20 (71.4) | No | 10 (35.7) |
| No | 8 (28.6) | Yes | 18 (64.3) |
| Progression | | Arthralgia | |
| No | 26 (92.9) | No | 10 (35.7) |
| Yes | 2 (7.1) | Yes | 18 (64.3) |
| Death | | Cough | |
| No | 27 (96.4) | No | 25 (89.3) |
| Yes | 1 (3.6) | Yes | 3 (10.7) |
| Decrease in EF | | Elevated liver enzymes | |
| No | 27 (96.4) | No | 23 (82.1) |
| Yes | 1 (3.6) (15. Ay) | Yes (Grade 1) | 5 (17.9) |
| Allergic reaction | | Hyperbilirubinemia | |
| Yes | 2 (7.1) | No | 27 (96.4) |
| No | 26 (92.9) | Yes (Grade 1) | 1 (3.6) |
| Neutropenia | | Neuropathy | |
| No | 8 (28.6) | No | 20 (71.4) |
| Yes | 20 (71.4) | Yes | 8 (28.6) |
| Neutropenia Grade | | Neuropathy grade | |
| Grade 1 | 9 (45.0) | Grade 1 | 2 (25.0) |
| Grade 2 | 6 (30.0) | Grade 2 | 1 (12.5) |
| Grade 3 | 4 (20.0) | Grade 3 | 5 (62.5) |
| Grade 4 | 1 (5.0) | | |
| G-CSF administration | | Hypocalcemia | |
| No | 11 (39.3) | No | 27 (96.4) |
| Yes | 17 (60.7) | Yes | 1 (3.6) |
| Neutropenic fewer | | Lacrimation | |
| Yes | 1 (3.6) | Normal | 13 (46.4) |
| No | 27 (96.4) | Decreased | 15 (53.6) |
| Thrombocytopenia | | Diarrhea | |
| No | 25 (89.3) | No | 24 (85.7) |
| Yes (Grade 1) | 3 (10.7) | Yes (grade 1) | 4 (14.3) |
| Mucositis | | Rash | |
| No | 21 (75.0) | No | 26 (92.9) |
| Yes | 7 (25.0) | Yes (grade 1) | 2 (7.1) |
| Mucositis grade | | | |
| Grade 1 | 6 (85.7) | | |
| Grade 2 | 1 (14.3) | | |

G-CSF, Granulocyte colony stimulating factor; EF, ejection fraction

When the adverse event profile was examined, the most common side effects with a decreasing order were as follows; fatigue (75%), arthralgia/myalgia (64.3%), decrease in lacrimation (53.6%), alopecia (53.6%), nausea (46.4%), asthenia (39.3%), neuropathy (28.6%), neutropenia (28.6%), elevated liver enzymes (17.9%), thrombocytopenia (10.7%), allergic reaction (7.1%), mucositis (3.6%), decrease in Ejection Fraction (EF) (3.6%). However, grade 3 and 4 toxicity were observed to be very infrequent [neutropenia; grade 3 in 4 (14%) patients and grade 4 in 1 (3.6%) patient, neuropathy; grade 3 in 5 (17.8%) patients]. There was no drug-related death, treatment discontinuation, or treatment interruption. Dose reduction was required for docetaxel in 20 (71.4%) patients and G-CSF was administered in 17 (60.7%) patients. Side effect profile was shown in Table 2.

## Discussion

Approximately 25% of all BC cases are HER2 positive. Although HER2 positivity is associated with poor prognosis, the development of anti-HER2 therapies has led to significant progress in the treatment of HER2-positive BC patients. Trastuzumab-a monoclonal antibody targeting HER2 has been used in the treatment of metastatic and early stage of HER2-positive BC cancer for about 20 years. Although PFS and OS are significantly better in patients treated with trastuzumab, progression and recurrence in this population still remain a therapeutic challenge.

Pertuzumab inhibits HER dimerization by binding to a HER2 epitope which is different from the epitope that trastuzumab usually bounds, hence resulting in an enhancement in the effect of trastuzumab (13). The efficacy and safety of the pertuzumab in combination with trastuzumab + docetaxel was shown in two phase II studies and in one pivotal phase III study (12, 14, 15). In this study, we aimed to evaluate the efficacy and safety of this new anti-HER2 drug in a patient group from our own centers. Since the median follow-up time in our study was 10.4 months, it was not sufficient to perform an optimal survival analysis. There were 2 deaths and 1 progression in whole population. Nevertheless, the continuation of the response in the remaining 25 patients suggests that the PFS and OS may be able to reach to 19 months and 56 months, respectively, as shown in its phase III study (16).The CLEOPATRA- an International, randomized, and placebo-controlled pivotal phase III study randomized 808 patients in a 1:1 ratio to receive either pertuzumab + trastuzumab + docetaxel or placebo + trastuzumab + docetaxel combination. The trial showed a significantly better PFS and OS durations in the pertuzumab containing arm (19 months versus 12 months, and 56.5 months versus 40.8 months, respectively) (12, 16). The mean age of the patients in our study was 47 years, which was younger than that of those in the CLEOPATRA study. Moreover, hormone receptor positivity in our cohort was found 78.6% compared to 47% reported in phase III study (12). The median number of docetaxel cure was 7 in our study, similar to that in its phase III trial. However, 70% of patients in our study required dose reduction for docetaxel compared to 26% of those in CLEOPATRA study. The median cycle number of pertuzumab + trastuzumab combination (with or without docetaxel) in our study was 18 versus 24 cycles in its phase III study (12). In another retrospective Italian study, the median number of docetaxel cycle was 7, similar to our findings. Likewise, the rate of dose reduction for docetaxel in Italian study was found in a higher rate (85%) than that in the CLEOPATRA study, indicating similar ratios to our real life data. However, unlike our analysis, the median cycle number of pertuzumab + trastuzumab combination (with or without docetaxel) was 8 (17). When considering the side-effect profile, it was observed that there were differences in the frequency of side-effects in our study compared to those reported in phase III clinical study and other retrospective studies. To illustrate, in the CLEOPATRA study, diarrhea was the most common side effect, with a rate of 66.8% compared to 14.3% in our study. The most frequent side effects in our study were fatigue and arthralgia/myalgia, with the rates of 75% and 64.3, respectively compared to 37.6% and 15% in CLEOPATRA, 26% and 6% in a retrospective analysis by Placido et al., respectively (12, 17). In our study, neuropathy occurred in 8 (28.6%) patients, with the 5 (17.8%) of them being grade 3 compared to 11 (2.7%) patients in CLEOPATRA phase III trial, 60 (18.4%) patients in a retrospective analysis by Esin et al., and 89 (33.5%) patients in another study including 266 patients (18, 19). As compared with literature, hematological side effects in our study were observed to be relatively at low rates, with 3 (10.7%) of the patients experiencing grade 1 thrombocytopenia compared to 25 (7.8%) of those in the study by Esin et al, with only 3 of them being grade 3-4 (19). In our study, neutropenia was seen in 8 (28.6%) patients, with 3 of them being grade 1-2 (10.7%), 4 (14%) grade 3, and 1 (3.6%) grade 4 versus 215 (52.8%) patients in CLEOPATRA trial, and 23 (15%) patients in Italian study (17). Robert et al. reported the incidence of neutropenia and

neutropenic fever in their study as 24.9% and 2.3%, respectively (18) compared to 35.7% and 4.1% in the retrospective study by Esin et al. (19). As shown in our study, the rates of neutropenia and febrile neutropenia were found to be at lower rates in other studies assessing the real life data than those found in phase III CLEOPATRA trial. When considering cardiac side effects, the rate of EF decrease was observed to be similar to those reported in previous studies, with 3.6% of our patients experiencing a decrease in EF versus 3% of those in a phase II trial that investigates cardiac side effects in 69 patients. This rate was only 1% in NEOSPHERE trial that investigated the efficacy of pertuzumab in neoadjuvant setting. In a retrospective study by Robert et al., 2 (0.8%) patients had Left Ventricular Dysfunction (LVD), whereas 8 (2.5%) patients experienced LVD in the study by Esin et al. (18-21).

The major limitations of our study were the small sample size, short follow-up time, and its retrospective nature. Nevertheless, our findings were similar to those reported in other retrospective evaluations which included greater number of patients. Furthermore, "the fact that only 2 patients developed disease progression at a median follow-up time of 10 months and that our survival rates were favorable" indicate that our findings are likely to be consistent with other studies, even if PFS and OS did not reach to the median value because of short follow-up period. In conclusion, pertuzumab in combination with trastuzumab + docetaxel is safe and effective in the treatment of HER2-positive metastatic BC. Herein we intended to present our own real life data from two centers. Moreover, in upcoming periods, we would like to report our long-term findings, with a larger number of patients.

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