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Short term real world safety data of pertuzumab use in HER2 targeted treatment of metastatic breast cancer

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ABSTRACT

Introduction: With the development and widely use of HER2 targeted therapies, HER2 expressing metastatic breast cancer have no longer dismal prognosis as once expected. The combination of HER2 targeted therapies with chemotherapatic agents prolongs overall survival. Pertuzumab is a new monoclonal antibody molecule that binds to the extracellular portion of HER2 and works by inhibiting homo- and heterodimerization. The aim of this study is to document the real life data of toxicities seen in metastatic breast cancer patients treated with first line trastuzumab-pertuzumab combination therapy.
Material and method: A retrospective review of 26 cases from the medical oncology patient registry was conducted to include the dates October 2016 through December 2017. The number of cycles of treatment and doses, adverse events, dose changes and course delays, reasons for treatment change and types of second line treatments are noted. The imaging and laboratory test results were obtained from the electronic registration system. The cumulative toxicity incidence was accepted as the primary endpoint.
Results: The median age of the 26 cases was 54 years. The median cycle number of pertuzumab and docetaxel treatments were 9 and 7, respectively and the median duration of pertuzumab therapy was 6.75 months. As of the date of last follow-up, 80.7% of the cases were still under treatment. There was a total of 6 cases of delay in treatment, of which five were due to neutropenia, while in one case the cause was diarrhea. When the adverse events were examined, at least one side effect (excluding alopecia) was observed in 16 patients and 7 cases had no toxicity except alopecia. In terms of constitutional symptoms, eight of the 19 patients had grade 1 fatique, one case had itching, and three patients had asthenia. Hematologic toxicity was seen in twelve cases and all had at least grade 1 leukopenia. Grade 3-4 febrile neutropenia occurred only in one case. Left ventriculer ejection fraction was measured stable for all of the cases, none of them experienced any significant decrease.
Conclusion: According to the results of this retrospective analysis, the use of pertuzumab-trastuzumab-docetaxel in the first line treatment of HER2 expressing metastatic breast cancer had good safety profile and had positive clinical results and paralleled with the results of the pivotal study.

1. Introduction

Breast cancer is the most common malignancy diagnosed globally and according to SEER data it is the leading maligancy associated with cancer-related deaths in women.[1] According to the statistics of the Turkish Public Health Institution Cancer Department in Turkey, breast cancer comes first among the age standardized cancers in women.[2] Although metastatic breast cancer has a low probability of cure; recently, significant progress has been made in the treatment.

One of the important decision mechanisms in the treatment of breast cancer is the determination of the cellular expression of human epidermal factor-2 (HER2) receptor. Her is a glycoprotein transmembrane epidermal growth factor receptor (EGFR) with tyrosine kinase activity. When its role in breast carcinogenesis has been discovered, first it was shown to be associated with a high risk of recurrence and poor overall prognosis.[3–6] However, with the development and use of HER2 targeted therapies, HER2 expressing

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tumors have no longer dismal prognosis as once expected. The combination of HER2 targeted therapies with chemotherapatic agents prolongs overall survival.[4]

Today, two newly developed molecules used in HER2 targeted therapy have opened new horizons in the treatment of HER2 expressing breast cancer. Pertuzumab (Pert) is a monoclonal antibody that binds to the extracellular portion of HER2 and works by inhibiting homo- and heterodimerization. The second agent is the antibody-chemotherapy conjugate named as Ado-trastuzumab emtansin (T-DM1).

Evidence of the use of triple combination pertuzumab plus trastuzumab plus chemotherapy in metastatic breast cancer is based on the results of the CLEOPATRA study.[7,8] In this phase-3 study involving 808 patients with a median of 19 months follow-up; a benefit in 3 year overall survival (OS) as 80% and in progression free survival (PFS) as 19 months has been found, respectively. Despite these positive results, neither single agent trastuzumab nor combination with pertuzumab is immaculate in terms of side effects.

When used in combination with trastuzumab chemotherapy, important side effects (>10%) with increasing order include infusion reaction, headache, infections, congestive heart failure (CHF) and decrease in left ventricular ejection fraction (LVEF). When pertuzumab is added to the treatment with trastuzumab, toxicity also increases (9). As a result of this combination, the major side effects observed in increasing order were diarrhea (67%–47%); neutropenia (50%–53%); rash (34%–24%) and dry skin (from 4% to 10%). Severe side effects included an increase in the incidence of febrile neutropenia from 8% to 14%. However, there was no statistically significant difference in the rate of a decrease in LVEF (1% vs 2%).

This study aimed to document the real life data of toxicities seen in metastatic breast cancer patients treated with first line trastuzumab-pertuzumab combination therapy in our center.

2. Material and methods

Patients who were diagnosed with metastatic breast cancer in our hospital and had an ECOG performance score of 0–1 and who had not previously been treated with trastuzumab for metastatic disease were included in this study. Pertuzumab was licensed in Turkey in February 2016 and has been included in reimbursement from October 2016. Therefore, a retrospective review of cases from the medical oncology patient registry was conducted to include the dates October 2016 through December 2017. Patients who received at least one course of pertuzumab were included. Clinical, demographical and histopathological characteristics of the cases were retriewed from patient files and electronic registration system. The number of courses and doses they take, adverse effects, dose changes and course delays, reasons for treatment change and types of second line treatments are noted. The imaging and laboratory test results were obtained from the electronic registration system and the changes observed while receiving pertuzumab were noted. Routinely performed transthoracic echocardiography (TTE) results, in order to investigate cardiac side effects in the follow-ups, were recorded in the database.

Chemotherapeutic agents were administered once in a 3-week chart and was continued until progression or unacceptable toxicity was experienced, and treatment was also stopped if the patient refused the treatment. Paclitaxel was administered (80 mg/m^2) weekly and docetaxel (75 mg/m^2) was administered once in 21 days; trastuzumab (Tra) was administered at a dose of 6 mg/kg and pertuzumab was administered with a bolus dose of 840 mg followed by 420 mg once in 21 days.

Cardiac monitorization was performed by a baseline evaluation with left ventricular ejection fraction measurement in every 4 courses (or in every 3 months).

The beginning of the Pertuzumab administration was accepted as the index date and all calculations were made accordingly. The progression-free survival was calculated as the duration from the index date until the occurrence of progression or death. Advers events were recorded between the index date and thirty days after the last dose of pertuzumab or the last data recording time.

This study was planned as retrospectively. The cumulative toxicity incidence was accepted as the primary endpoint. The overall survival rate and progression-free survival rates were accepted as secondary endpoints, as follow-up durations were limited.

The data were analyzed using the SPSS® v.20 statistical program. The safety margin was accepted as 95% throughout the study. Kaplan-Meier method was used for survival analysis and cox-regression model for multivariate analysis.

3. Results

Between September 2016 and July 2017, there were a total of 26 female patients in our center who were administered pertuzumab + trastuzumab combination chemotherapy for metastatic breast cancer. The youngest patient was 32 and the oldest patient was 69 years old. The median age of the cases was 54 years. Only three cases had previously received anthracycline chemotherapy with breast cancer diagnosis and 23 patients had de-novo metastasis. Five patients had comorbid disease, four of which were hypertension and three have diabetes mellitus (DM). Drugs used by these patients for comorbid diseases were studied in terms of drug interaction and no interaction was detected. Clinical and demographic characteristics are shown in Table 1.

Patient who received the shortest treatment had 2 courses of pertuzumab combination therapy and the longest treatment was consisted of 23 courses. The median cycle number of pertuzumab and docetaxel treatments were 9 (2–23) and 7 (2–10), respectively and the median duration of pertuzumab therapy was 6.75 months (1.5–17.2). As of the date of last follow-up, 80.7% of the cases were still under treatment. In two cases, pertuzumab was discontinued due to progression, one case left treatment at own will, and one case died due to cancer. There was a total of 6 cases of delay in

Table 1
The baseline clinical and demographic data.

Characteristics	N = 26
Median age (year, range)	57 (32–69)
Median duration of metastatic disease diagnosis (months)	1,7 (1.3–2.5)
No of patient group over 65 years	2 (7.7%)
ECOG	
0	18 (69.2%)
one	8 (30.8%)
Hormone receptor status	
ER or PR positive	5 (19.2%)
ER/PR negative	7 (26.9%)
ER and PR positive	14 (53.8%)
Metastasis localization	
Brain + Liver + Lung	2 (7.7%)
Lungs	2 (7.7%)
Lung + Bone	5 (19.2%)
Lung + Lymph node	4 (15.4%)
Liver	1 (3.8%)
Liver + Lymph node	6 (23.1%)
Liver + Bone	4 (15.4%)
Liver + Lung	2 (7.7%)
Chemotherapy Regimen	
Docetaxel	23 (88.5%)
Paclitaxel	3 (11.5%)

treatment, of which five were due to neutropenia, while in one case the cause was diarrhea.

When the adverse events were examined, Eighteen patients had at least one adverse event, in four of them alopecia was the sole toxicity and in rest of them alopecia with addition of other adverse events were occurred. There was no transfusion reaction in any case. In terms of constitutional symptoms, eight of the 26 patients had grade 1 fatique, one case had itching, and three patients had asthenia. During the follow-up period, all patients had total alopecia. Myalgia was observed in two cases as grade 1 and arthralgia was observed in two cases. One case was investigated for nonspecific pharyngitis, and it was observed that it improved without treatment. One case complained of nonspecific cough, no etiology was ascertained and the cough improved without any treatment. Antiemetic prophylaxis was performed in all patients and no vomiting was observed with this treatment, but three cases had nausea. There were no patients with mucositis, whereas diarrhea was observed in 4 cases. In one case, grade 3 diarrhea was seen. This case necessitated a 5 days delay in treatment. After supportive therapy, the treatment was resumed at the same dose and diarrhea did not recur. Other diarrhea cases were at grade 2 level. While rash was observed in three cases, the severity of rash was in the order of grades 1–2 and 3.

Hematologic toxicity was seen in twelve cases and all had at least grade 1 leukopenia. Nine of these cases needed granulocyte colony-stimulating factor (GCSF). Grade 3-4 febrile neutropenia occurred only in one case. This case was already using GSCF and the treatment was continued with secondary GSCF prophylaxis. One patient experienced grade 1 thrombocytopenia.

Six patients had elevated transaminase levels at grade 1 level which did not require dose reduction or delay. Hyperbilirubinemia was not observed.

Symptoms of neuropathy were present in seven cases. Only one case experienced grade 3 neuropathy and paliative treatment of neuropathy was required. In other patients, grade 1 neuropathy was observed.

At the time of diagnosis and during the treatment, all the patients who were followed up with serial echocardiography had normal findings at the beginning of the treatment and the decrease in the ejection fraction was not experienced in any patient.

A summary of the observed side effects are presented in Table 2.

The median OS and PFS were not reached within median follow-up of 6,8 months (1,5–17,3). In the first 3-months treatment responses, 71.4% (15 cases) had at least partial response and 23.8% had stable disease (5 cases), one case succumbed to death after 2 cycles of treatment due to progression. Accordingly, the clinical benefit rate after 3 months of treatment was found to be 95.2%. Among the patients who completed six months of treatment, the percentage of cases with at least stable disease response was 94.1%. One patient had stable disease after three months of treatment then had partial response after sixth months.

When the pathology of the cases were examined, it was seen that hormone receptors were strongly positive in fourteen cases, three cases had negative estrogen receptor (ER) but positive progesterone receptor (PR) and two cases were ER positive-PR negative and seven cases were ER-PR negative. Contrary to the CLEOPATRA study, in four cases, antihormonal therapy has been added to pertuzumab-trastuzumab combination therapy when docetaxel therapy was discontinued.

Table 2
Adverse events grading and frequencies.

	Grade1	Grade 2	Grade 3	Total
	n (%)	n (%)	n (%)	n (%)
Fatigue/Asthenia	8 (30.8)	–	–	8 (30.8)
Nausea	3 (11.5)	–	–	3 (11.5)
Peripheral Neuropathy	6 (23.1)	–	1 (3.8)	7 (26.9)
Myalgia	2 (7.7)	–	–	2 (7.7)
Arthralgia	1 (3.8)	–	–	1 (3.8)
Rash	1 (3.8)	1 (3.8)	1 (3.8)	3 (11.5)
Itching	1 (3.8)	–	–	1 (3.8)
Diarrhea	–	3 (11.5)	1(3.8)	4 (15.4)
Transaminase elevation	6 (23.1)	–	–	6 (23.1)
Hematologic Adverse Events				
Febril Neutropenia	–	–	2 (7.7)	2 (7.7)
Neutropenia	3 (11.5)	–	–	3 (11.5)
Anemia	10 (38.5)	3 (11.5)	–	13 (50.0)
Thrombocytopenia	2 (7.7)	–	–	2 (7.7)

4. Discussion

Pertuzumab is a humanized monoclonal antibody that acts by binding to the extracellular portion of the HER2 receptor via a different epitope from trastuzumab. Unlike trastuzumab, it acts not only by homologous dimerization of HER2 but also by heterologous (with her-3 or her-1) dimerization.[9] At the same time, pertuzumab binds to the subdomain of the HER2 receptor to provide antibody mediated cytotoxicity. The combination of pertuzumab with trastuzumab produces a more effective antitumoral effect by establishing a more detailed pressure on her pathway.[10] This activity is attenuated by the inhibition of mitogen-activated protein kinase pathway (MAPK) and phosphotidylinositol pathway (PI3K).

When used as a single agent, Pertuzumab has limited clinical activity in the case of progression under treatment with trastuzumab.[11] However, in a phase-2 study involving progressive patients under trastuzumab treatment, the combination of pertuzumab-trastuzumab achieved an objective response rate of up to 24% and a clinical benefit rate of 50%; median progression-free survival (PFS) was 5.5 months.[12] The main clinical efficacy study of the Pertuzumab is the CLEOPATRA trial. In this study, where the pert-tra-docetaxel combination was compared with tra-docetaxel in the first line therapy of metastatic breast cancer, PFS of 18.5 months–12.4 months was obtained in pertuzumab area (Hazard ratio-HO-0,62; $p < .001$).[8] Based on these results, in 2012 it was approved by the US Food and Drug Administration (FDA) for the first-line treatment of metastatic breast expressing HER2.

In addition to this clinical benefit advantage, it has been shown that pertuzumab is generally well tolerated in clinical trials. The first safety data is based on BO17929 and TOC3487 phase-2 trials in which the pert-tra combination was tested without chemotherapy.[12,13] In the first study, adverse event rates were mild to moderate. The most common toxicities were diarrhea (64%), asthenia (33%) and nausea (27%). There was an increase in more than grade 3 diarrhea and febrile neutropenia risk (National Cancer Institute General Terminology Criteria, CTCAE). In TOC3487 study, a decrease in left ventricular ejection fraction (LVEF) was found in 54% of the cases. Grade 3 LVEF reduction was occurred in one case, grade 2 in two cases and grade 1 in one case. All of these cases received anthracycline and trastuzumab as an adjuvant treatment previously. For this reason, this study was prematurely terminated due to cardiac safety reasons before inclusion of planned 37 patients.

According to the results of the CLEOPATRA study, the addition of pertuzumab to the combination of trastuzumab and docetaxel did not cause additional side effect profile. When compared with the placebo, the most common adverse events in the pertuzumab arm were diarrhea with 66% vs. 46%; followed by rash (33% vs. 24%) and mucositis and dry skin. Febrile neutropenia frequency increased to 13.8% vs. 7.6%. Contrary to expectations, the frequency of cardiac events in the control group was found to be higher by 16.4% vs.

14.5%. The most common cardiac adverse event was left ventricular systolic dysfunction; 8.3% in the control group and 4.4% in the pert group. Symptomatic LVSD was observed in 1.8% of the control group and 1% of the pert group, but improved during the analysis of the study. The rate of more than 10% reduction in the ejection fraction was higher in the control group than in the pert group and was found to be 6.6% vs. 3.8%. Of these cases, 72% of the control group and 86.7% of the pert group improved to at least 50% of the ejection fraction.[14]

The main focus of this current study is the early results of the experience with Pertuzumab, which received a license in Turkey in February 2016 and a reimbursement in October 2016. Although our center is amongst the leading high volüme medical oncology centers in Turkey, the duration of treatment is limited and the median events for survival rates have not yet been reached and therefore the results are immature for survival analysis. For this reason, this retrospective research aimed to investigate the short term real-life safety data of pertuzumab.

When the adverse event rates were examined, it was observed that the most common side effect was alopecia, fatigue and transaminase elevation regardless of grade. The most common grade 3 and severe side effects were diarrhea, febrile neutropenia and neuropathy. Another important point is that all these serious adverse events have been encountered during docetaxel use. The results of this study seem to have a similar incidence when compared to phase-2 and the phase-3 studies which lead to the approval of Pertuzumab. When examined for cardiac safety, there was no LVEF and no additional cardiac adverse events in this trastuzumab naive patient group in serial follow-ups. However, it should not be forgotten that this research is based on retrospective information analysis and may be biased due to low level of reported adverse events.

The survival results of this study have not yet matured due to the limited time of follow-up periods and the number of incomplete events. However, in the first 3 months and following 6 months, the clinical benefit rate was 95.2% and 94.4%, and this was better than the phase 3 study. Careful selection of the cases in our clinic may have a positive effect on the better outcome.

5. Conclusion

According to the results of this retrospective analysis, the use of pertuzumab-trastuzumab-docetaxel in the first line treatment of HER2 expressing metastatic breast cancer had good safety profile and had positive clinical results and paralleled with the results of the pivotal study.

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