Trastuzumab, Pertuzumab, and Docetaxel as the First Line for HER-2-Positive Metastatic Breast Cancer among Arabs

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Keywords

Pertuzumab · Metastatic breast cancer (MBC) ·
HER-2-positive MBC · Dual targeted therapy

Abstract

Introduction: Human epidermal growth factor receptor 2 (HER-2) targeted therapy regimens can improve tumor response in HER-2-positive metastatic breast cancer (MBC), with overall survival benefits. **Objective:** We evaluated the efficacy of dual HER-2 blockade combined with chemotherapy for HER-2-positive MBC patients as a first-line therapy in our patient population. **Patients and Methods:** We identified 75 patients at King Faisal Specialist Hospital and Research Center that received trastuzumab, pertuzumab, and docetaxel as a first-line therapy in HER-2 positive MBC in 2013–2016. **Results:** Median age at diagnosis was 45 years; 54.7% were estrogen receptor (ER)-positive. 10% of patients presented with only bone metastasis. The median follow-up time was 36 months with an objective response rate of 74.7% (complete response [CR] 18.7%; partial response [PR] 56%). The 5-year progression-free survival (PFS) and overall survival (OS) were 21% and 71.9% respectively, with a median PFS

of 36 months (95% confidence interval [CI] 23.6–48.4). The 5-year OS for ER-negative and ER-positive patients was 93.9% and 59.4% respectively ($p = 0.189$); 23 patients experienced grade 1/2 toxicity and 2 patients had grade 3/4 toxicity. In terms of OS and PFS, the site of metastasis did not make any significant difference. **Conclusions:** First line pertuzumab, trastuzumab, and docetaxel for HER-2-positive MBC patients was found to be an effective and safe therapy in the Saudi population. This finding was consistent with the results seen in the CLEOPATRA trials. © 2020 S. Karger AG, Basel

Introduction

Anti-human epidermal growth factor receptor 2 (HER-2) directed therapy is established as a standard of care for patients with HER-2-positive breast cancer. Dual HER-2 blockade with pertuzumab used in addition to trastuzumab has been shown to improve progression-

The abstract was presented at the 16th St. Gallen International Breast Cancer Conference, Vienna, Austria on 22–23rd March 2019.

free survival (PFS) by 6.1 months, as well as increase overall survival (OS) by 15.7 months, with tolerable toxicity in patients in the West [1–3]. This efficacy has also been reported in the neoadjuvant setting [4].

Since these international studies were not conducted on our ethnic group in Saudi Arabia, we aimed to evaluate the safety and efficacy of trastuzumab, pertuzumab, and docetaxel in our cohort of patients as a first-line therapy in the metastatic setting of HER-2-positive patients, and to then compare our results with international data in terms of toxicity and survival outcome.

Methods

This was a retrospective, observational study carried out in a single institute, which is one of the largest tertiary care centers in the Middle East. Patients who received trastuzumab, pertuzumab, and docetaxel as first-line therapy for de novo metastatic or relapsed HER-2-positive breast cancer were retrospectively identified for the period between May 2013 and September 2016. Pertuzumab was approved as a formulary medication in our institute at the time this study was conducted, and our hospital guidelines adjusted and updated accordingly.

Inclusion Criteria

- An age of ≥ 18 years.
- A left ventricular ejection fraction (LVEF) $\geq 50\%$ as assessed by echocardiography or a multigated acquisition (MUGA) scan.
- A normal complete blood count and differentials (CBCD), and renal and hepatic profiles; all were assessed for response and toxicities.
- HER-2 positivity confirmed by immunohistochemistry (IHC) and/or fluorescence in situ hybridization (FISH) analysis.

Data Collection

Data were extracted from the electronic health records database. We reviewed each medical record, looking at demographics (age, gender, and comorbidities at presentation); presenting symptoms relating to the tumor; and, in the case of relapse, the type of previous therapy received in the neoadjuvant setting (including trastuzumab-, hormone-, and taxane-based therapy). Complete lab evaluation including CBCD, renal and hepatic profiles, and CA15.3 was done. To determine the basal cardiac function, baseline LVEF was estimated using echocardiography or a MUGA scan, which was done routinely to determine any cardiac toxicity that occurred from the use of the 2 monoclonal antibodies. We also looked at therapy details, the agents used in each line of therapy, the response, and the overall duration of treatment. If patients stopped any line of therapy, then the reason for the change, if any, was also recorded and included toxicity, e.g., neutropenia, allergic reactions, etc. Tumor characteristics such as hormone receptor status and the type of metastasis (visceral, non-visceral, or both) were also noted.

All the tumors were assessed every 3 months as per standard clinical guidelines for response to therapy using the appropriate imaging modality (bone scan or computed tomography [CT]) to assess the response in terms of progression or improvement. Lastly, the date of the last follow-up visit and disease status at this visit were recorded. Data were collected from the period 2013–2016, i.e., for a total of 4 years. Patient and tumor characteristics can be found in Table 1.

Table 1. Patient and clinical characteristics

	CLEOPATRA <i>n</i> = 402	Our study <i>n</i> = 75
Age, years		
Median	54	45
Range	22–82	27–98
Baseline ECHO		
$>55\%$	n.a.	58 (77.3%)
50–55%	n.a.	17 (22.7%)
Presentation		
De novo	218 (54.2%)	54 (72%)
Relapse	184 (45.8%)	21 (28%)
Hormone receptor ^a status		
Positive	189 (47%)	41 (54.7%)
Negative	212 (53%)	34 (45.3%)
Disease type at screening		
Visceral	314 (78%)	44 (58.7%)
Non-visceral	88 (22%)	8 (10.7%) ^b
Both	n.a.	23 (30.7%)
Concordant metastasis		
Yes	n.a.	20 (26.7%)
No	n.a.	15 (20%)
Not available	n.a.	40 (53.3%)
CNS metastasis (brain)		
Yes	n.a.	5 (6.7%)
No	402 (100%)	70 (93.3%)
Prior (neo)adjuvant therapy		
Yes	184 (46%)	21 (28%)
No	218 (54%)	54 (72%)
(Neo)adjuvant therapy type		
Trastuzumab	47 (12%)	21 (28%)
Anthracycline	150 (37%)	21 (28%)
Taxane	91 (23%)	21 (28%)
Hormone	106 (26%)	8 (11%)

ECHO, echocardiography; CNS, central nervous system; n.a., not available.

^a Estrogen receptor or progesterone receptor.

^b Patients with bone-only metastasis.

Procedures

Trastuzumab and pertuzumab were given in the first cycle at a dose of 840 mg + 8 mg/kg, and in the subsequent cycles at 420 mg + 6 mg/kg, with no later dose reduction. Docetaxel was started at 75 mg/m² every 21 days, also with no subsequent dose reduction; it was given for 6–8 cycles, stopped, and then followed by maintenance pertuzumab and trastuzumab as well as hormone treatment for the hormone-positive subgroup according to our local guidelines. All drugs were given intravenously. Pertuzumab was only stopped in the case of disease progression or intolerable side effects. Assessment of the response to treatment was done by radiological imaging, usually a CT/bone scan for bone metastasis if clinically indicated, according to the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 [5]. Estrogen receptor (ER), progesterone receptor, and HER-2 were determined on the pretreatment biopsy by IHC. HER-2 was considered positive if $\geq 10\%$ of tumor cells stained for ER and/or progesterone receptor. HER-2 status was determined by IHC and confirmed with FISH if it was equivocal (2+) by IHC; a FISH ratio of >2 was considered positive [6].

Fig. 1. Kaplan Meier graph for overall survival. 1, positive receptor status; 2, negative receptor status; Cum, cumulative.

Fig. 2. Kaplan Meier graph for progression-free survival. 1, positive receptor status; 2, negative receptor status; Cum, cumulative.

Statistical Methods

The χ^2 test was used to compare the categorical variables expressed as n (%). Medians were used for the assessment of continuous data as in the case of PFS. OS was defined as the time taken from the initiation of therapy to the death of the patient. PFS was defined as the time from the initiation of therapy to the first evidence of progression assessed by radiological or clinical means. Both OS and PFS were calculated for the overall population and the Kaplan-Meier method was used to approximate the distribution of OS and PFS in the subgroup analysis for hormone receptor-positive and hormone receptor-negative disease as well as for relapse versus de novo disease. Log-rank (Mantel-Cox) test was performed to analyze a difference, if any, with the use of trastuzumab, pertuzumab, and docetaxel for patients with positive versus negative hormone receptor disease, site of metastasis, or relapse versus de novo metastatic disease, all in relation to PFS or OS. $p \leq 0.05$ was considered statistically significant. Response to treatment was defined using RECIST v1.1 [5]. All calculations were performed using SPSS software v20.

Results

We identified 75 patients that met the inclusion criteria. Median age at diagnosis was 45 years (27–98). The median follow-up time was 36 months (range 8–92). All patients received 6–8 cycles of docetaxel with HER-2 targeted therapies, and then continued dual targeted maintenance therapy. The median number of maintenance cycles of dual targeted therapy was 21. Of the 75 patients evaluated, 14 (18.7%) showed a complete response (CR) and 42 (56%) a partial response (PR), 8 (10.7%) had stable disease (SD) and 11 (14.7%) progression of disease (PD). The objective response rate was 74.7%. The 5-year OS was found to be 71.9% with a median OS not yet reached

Fig. 3. Kaplan Meier graph for overall survival based on hormone receptor status. 1, positive receptor status; 2, negative receptor status; Cum, cumulative.

(Fig. 1). The 5-year PFS was found to be 21% with a median PFS of 36 months (95% confidence interval [CI] 23.6–48.4) (Fig. 2).

In terms of tumor biology, 41 patients (54.7%) had triple-positive hormone receptor status and 34 (45.3%) had ER/progesterone receptor-negative status. The 5-year OS for hormone receptor-negative patients was 93.9%; for hormone receptor-positive patients, it was 59.4% ($p = 0.189$) (Fig. 3). Hormone receptor-negative patients had

Fig. 4. Kaplan Meier graph for progression-free survival based on hormone receptor status. 1, positive receptor status; 2, negative receptor status; Cum, cumulative.

Table 2. Toxicity profile

Toxicity	<i>n</i> (%)
Hypertension	3 (4%)
Allergic reaction	5 (6.66%)
A drop in ejection fraction	12 (16%)
Thrombocytopenia/neutropenia	14 (18.6%)
Diarrhea	1 (2.3%)

a 5-year PFS of 21% and hormone receptor-positive patients a 5-year PFS of 23% ($p = 0.683$) (Fig. 4).

Forty-four patients (58.7%) had visceral metastases, 8 (10.7%) had non-visceral (bone only) metastasis, and 23 (30.7%) had both. An analysis was performed to compare the survival outcomes of patients with either visceral or non-visceral metastases, or both. OS and PFS were statistically insignificant at $p = 0.723$ and $p = 0.592$, respectively. Forty-five patients (60%) managed to receive second-line therapy upon progression, while 14 (18.6%) received a third line and more treatment regimens. There were 9 patients with primary refractory disease.

Twenty-three patients experienced grade 1–2 toxicity. There were 2 cases of grade 3–4 toxicity, one due to an allergic reaction and the other due to a drop in LVEF; treatment was stopped for both these patients. Refer to Table 2 for a detailed toxicity profile.

Twenty-one patients (28%) had disease relapse after a prior diagnosis of non-metastatic breast cancer (non-MBC) while 54 patients (72%) had de novo MBC. For a comparison between de novo and relapse patients' sur-

vival outcomes, OS and PFS were calculated. Median PFS was 37 months for de novo patients (95% CI 14.7–59.3 months) and 36 months for relapse patients (95% CI 21.4–50.6 months). Log-rank (Mantel-Cox) testing performed in both groups showed $p = 0.487$ for PFS and $p = 0.317$ for OS, indicating no statistically significant differences in survival in either group.

Discussion

Patients with HER-2-positive MBC are now showing a better prognosis with improved PFS and OS than patients with HER-2-negative disease due to HER-2 targeted therapies [7, 8]. The phase III CLEOPATRA trial with a median follow-up of 50 months showed that the addition of pertuzumab to trastuzumab and docetaxel significantly improved OS and PFS among HER-2-positive MBC patients. There was an added value of 15.7 months for OS (i.e., 56.5 vs. 40.8 months) and 6.3 months for PFS (18.7 vs. 12.5 months).

Our intention was to prove the efficacy of this combination protocol in our ethnic group, i.e., the Arab population ($n = 75$). The 5-year OS of our patients was 71.9% with the median OS not yet reached as >50% of the patients were still alive at the end of the study period. However, when comparing our 5-year OS (71.9%) with the CLEOPATRA trial's 4-year OS (57.6%), it was observed that our patients showed a better response. Furthermore, in our study, the median PFS was found to be 36 months, which is better than the 18.7 months demonstrated in the CLEOPATRA trial with 50 months of follow-up. Our data, along with the data of 2 other retrospective studies, show that the results of the CLEOPATRA trial can be replicated with similar, if not better, efficacy of this treatment regimen in a real-life setting [9, 10].

The difference in survival outcomes with those of the CLEOPATRA trials may be due to our patient population being younger, with a median age of 45 years (vs. 54 years in the CLEOPATRA trials). These younger patients probably had fewer comorbidities than the relatively older patient population in the CLEOPATRA trial. On the other hand, it has also been observed that breast cancer in younger women (<40 years) presents with a higher grade, i.e., triple-negative or HER-2-positive tumors, and these women also tend to present later, all adding to a poorer survival [11, 12].

The ECOG status of the patients started on this first-line therapy was 0–1. Furthermore, 72% of our patients were diagnosed with de novo disease and were consequently less prone to resistance. Lastly, the presence of brain metastases was one of the exclusion criteria of the CLEOPATRA trial. Five of our patients (6.7%) had brain metastases at baseline; 2 had PR, 2 had SD, and 1 had PD.

The use of pertuzumab for brain metastatic patients is thus questionable and needs further research. However, these differences did not seem to affect the efficacy profile of this therapy. In fact, our results confirm the usefulness of this dual targeted therapy as a first-line therapy in this group of patients, albeit a small sample.

The objective response rate of 74.7% in our study is almost comparable to other studies, such as 79% for the docetaxel group in the PERUSE study [13]. For the paclitaxel group, the objective response rate was higher (83%), but with reported unfavorable side effects like peripheral neuropathy. Our group also suffered from neutropenia (18.6%), i.e., higher than the 11% in the docetaxel group in the PERUSE study. Paclitaxel, the taxane component of this combination therapy, is thus a valid option only in selected patient populations.

In this study, fewer side effects were reported, but this is due to the retrospective nature. Nevertheless, no unexpected or serious toxicity occurred except in 2 patients that were reported to have experienced grade 3/4 toxicity, one due to allergy and the other due to a drop in LVEF. In the CLEOPATRA trials, the intervention group did not have an increase in rates of symptomatic or asymptomatic cardiac dysfunction [1–3]. In our study, the reported cardiac toxicity was higher at 16% (vs. 3.8% in the CLEOPATRA trials). One explanation for this may be alternating between echocardiography and a MUGA scan, with the latter being more sensitive as it measures the LVEF exactly without an estimation. Furthermore, in our study, even a trivial drop in LVEF was considered a cardiac toxicity. It is also relevant to note that the Arab population has a higher prevalence of both cardiovascular and coronary artery diseases, which could explain the lower threshold for cardiotoxicity from treatment [14, 15].

It has been observed in other studies that median survival is dependent on MBC subtype, with the shortest OS, i.e., 27 months, for ER-negative/HER-2-negative tumors, in comparison to 52 months for ER-negative/HER-2-positive tumors, 76 months for ER-positive/HER-2-negative/Ki67^{high} tumors, and 79 months for ER-positive/HER-2-negative/Ki67^{low} tumors [16].

Our results showed that, in the hormone receptor-negative subgroup, the 5-year OS was found to be 93.9%; in the hormone receptor-positive subgroup, it was 59.4%. Although not statistically significant, this trend indicates that ER-negative patients had a better OS in comparison to ER-positive patients. This is an unusual trend that was seen in our patients as it has previously been observed that ER-positive/HER-2 positive (88.7%) MBC patients had a longer OS than those with ER-negative/HER-2 positive (78.8%) MBC [17]. Presumably, factors such as small sample size, comorbidities, age, tumor size and degree of metastasis also play an important role in determining the prognosis.

De novo patients, being treatment-naïve, are generally thought to perform better than relapse patients who have previously received some form of neoadjuvant therapy. In our study, the neoadjuvant therapy differed from patient to patient as per the protocol at the time, with 8 patients receiving hormone therapy and all of them having previously received neoadjuvant trastuzumab ($n = 21$). After the diagnosis of relapse of disease, they were started on first-line therapy for metastatic disease with trastuzumab, pertuzumab, and docetaxel. However, our analysis showed no differences in OS or PFS between the de novo and relapse patients. One retrospective study showed that in patients with HER-2-positive MBC without prior treatment with trastuzumab had better clinical outcomes than those with prior treatment [18].

Our study suggests that patients receiving this regimen had a remarkable improvement in outcome (PFS and OS). The good clinical result obtained with the combination of trastuzumab and pertuzumab is likely due to the more comprehensive blockade with each monoclonal antibody targeting a distinctive receptor epitope. Pertuzumab binds to HER-2, but, unlike trastuzumab, it binds to the HER-2 subdomain II and thus prevents its dimerization. Due to the similar mechanisms of actions of the 2 drugs, they achieve a much more effective therapy than trastuzumab only; they inhibit receptor dimerization and suppress signaling, ultimately inhibiting the intracellular signaling cascade that promotes cell growth [19]. The effect of using pertuzumab alone was observed in the BO17929 study which showed that using trastuzumab along with pertuzumab resulted in better outcomes [20].

Updated results from the analysis of the CLEOPATRA trial that had a median follow-up of 99 months showed that with an addition of 4 years the OS hazard ratio was 0.69 (95% CI 0.58–0.82), thus favoring the intervention group. Median OS was 57.1 months in the intervention group and 40.8 months in the control group, i.e., a difference of 16.3 months. The 8-year OS rates were 37 and 23%, respectively. The overall safety profile remained consistent with the previous reports [21].

Strengths and Limitations

It should be kept in mind that our sample size was fairly small and so it is important to be cautious when interpreting our results. In addition, pertuzumab was used alongside trastuzumab and docetaxel and a 3-drug combination can add a great deal of complexity to the interpretation of the findings. Data on the toxic side effects was incomplete due to the retrospective design of the study. Lastly, the results seen are from a single institute from a retrospective cohort view and not from a randomized prospectively designed study and are thus susceptible to

bias and error. Valid comparisons can therefore not be made about the efficacy of pertuzumab with a control group. Further research with a larger population and a longer follow-up is warranted.

The strengths of this study should not be forgotten. Firstly, this paper outlines the outcomes of pertuzumab-based therapy for MBC in HER-2-positive patients in a real-life setting. With the current rapidly changing environment in medicine and new treatments being introduced just as swiftly as the updates in best practice, it is necessary to coherently reproduce their value in daily practice. Moreover, this retrospective study looked at long-term outcomes in the Saudi population, a population not included in the CLEOPATRA clinical trials, thus allowing our results to be more generalized to the Arab population despite the small sample size. Furthermore, this study showed that even though most of the patients had locally advanced heavy metastatic disease, they still had a generally good 5-year OS and PFS.

Conclusion

Our findings suggest that the efficacy seen with the addition of pertuzumab to trastuzumab and docetaxel for HER-2-positive MBC are consistent with the results of the CLEOPATRA trials. These findings in our patient population support the benefit of using this treatment regime in patients with HER-2-positive MBC in Saudi Arabia, but further study is warranted for more conclusive results.

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Statement of Ethics

This research project was conducted in accordance with the Declaration of Helsinki (2000), Good Clinical Practice Guidelines, and the policies and guidelines of the Research Advisory Council of the King Faisal Specialist Hospital and Research Center. It was approved by the medical ethics committee. The identity of the patients studied remained anonymous since no identifying data or protected health information were recorded. All data were password-secured to ensure confidentiality. Consent for publication was granted by the Office of Research Affairs according to institutional internal regulations. The Research Advisory Council has the right of access to the supporting records.

Disclosure Statement

All authors declare that they have no competing interests.

Funding Sources

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Author Contributions

K.S.: study concept and design and manuscript editing. A.H.M.: data acquisition and manuscript writing and editing. E.H.: manuscript writing and data analysis. A.A.B.: study concept and design, statistical analysis, and manuscript editing. D.A.: study design and data analysis and interpretation. A.M.E.: statistical analysis and data interpretation. T.A.-T.: study design and data acquisition, analysis, and interpretation. A.M.G., A.O., A.S.A., K.A.K., A.E., and A.A.: data acquisition, analysis, and interpretation.

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