فعالية (البيرتوزوماب+ التراستوزوماب) كخط علاجي أول عند مريضات سرطان الثدي النقيلي إيجابيات الـHER2

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الملخص

خلفية البحث وهدفه: إن البيرتوزوماب هو جسم مضاد أحادي النسيلة مؤنسن، يربط المجال خارج الخلية من مستقبل HER2 (المجال الفرعي II), وله تأثير مكمل لتراستوزوماب الذي يرتبط بمجالات HER2 المختلفة. عند إعطاء هذين الجسمين المضادين معاً فإنهما يؤديان إلى تثبيط مزدوج للمستقبل وتثبيط ديمرة ثنائيات المستقبل وكبح أكبر لنشاط الورم. هذه الدراسة هي الأولى من نوعها عن نتائج إعطاء هذين الجسمين المضادين كخط أول في سرطان الثدي المتقدم ايجابي HER2 في مستشفى البيروني الجامعي.

مواد البحث وطرائقه: تلقت المريضات المصابات بسرطان الثدي المتقدم موضعيا أو النقيلي إيجابي HER2 بيرتوزوماب وتراستوزوماب إضافة إلى العلاج الكيميائي (دوسيتاكسيل أو فينورلبين) كخط علاج أول حتى تطور الورم أو حدوث سمية لايمكن السيطرة عليها. كانت نقطة النهاية الأولية الاستجابة والفائدة السريرية.

النتائج: دُرست 65 مريضة خضعن للمعالجة وقُيّمت المعالجة، وكان معدل الفائدة السريرية ومعدل الاستجابة 95٪ و81.4٪ على التوالي. في المجموعات الفرعية، كان لدى المريضات فائدة سريرية مماثلة عند إعطاء علاج الخط الأول من docetaxel مقارنة ب vinorelbine بالمشاركة مع تراستوزوماب وبيرتوزوماب (96.7٪ مقابل 94٪، على التوالي).

الاستنتاجات: تظهر نتائجنا تحسنًا واضحًا في الاستجابة والفائدة السريرية عند إضافة بيرتوزوماب إلى تراستوزوماب والعلاج الكيميائي في المرضى الذين يعانون من سرطان الثدي النقيلي إيجابي HER2. يجب أن يؤخذ في الحسبان الفينورلبين عن طريق الفم في هذه المشاركة العلاجية.

الكلمات المفتاحية: سرطان الثدي؛ HER-2 إيجابي؛ النقيلي؛ بيرتوزوماب؛ دوسيتاكسيل؛ تراستوزوماب؛ فينورلبين.

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Efficacy of pertuzumab and trastuzumab as first line treatment in patients with HER2-Positive Metastatic Breast Cancer

Maher Saifo*

Abstract

Background & Aim: Pertuzumab, a humanized monoclonal antibody, binds the HER2 extracellular domain (subdomain II), and has a complementary action to trastuzumab that binds to different HER2 domains. These two antibodies, when given together, provide a dual inhibition of receptor dimerization and greater anti-tumor activity. This study is the first to report results of these two antibodies as first line in HER2+ MBC, at Albairouni university hospital.

Patients and methods: Patients with HER2+ locally advanced or metastatic breast cancer received pertuzumab plus trastuzumab plus chemotherapy (either docetaxel or vinorelbine) as first-line treatment until the time of disease progression or the development of unmanageable toxicity. The primary end point assessed the objective response and clinical benefit.

Results: In the intention-to-treat population of 65 evaluable patients, clinical benefit rate and objective response rate were 95% and 81.4%, respectively. In the subgroups, patients had similar clinical benefit with first-line treatment of docetaxel or vinorelbine combined with trastuzumab and pertuzumab (96.7% vs. 94%, respectively).

Conclusion: Our results show a pronounced improvement in objective response and clinical benefit when adding pertuzumab to trastuzumab, and chemotherapy in patients with HER2-positive metastatic breast cancer. Oral vinorelbine should be highly considered for this combination.

Key words: Breast cancer; HER-2 positive; Metastatic; Pertuzumab; Docetaxel; Trastuzumab; Vinorelbine.

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Introduction:

Overexpression or gene amplification of human epidermal growth factor receptor 2 (HER2) is a poor prognostic factor that occurs in approximately 20% of primary breast carcinomas.[1-3] HER2 is also a predictive factor for response to HER2-targeted therapies (Fig. 1).[4]

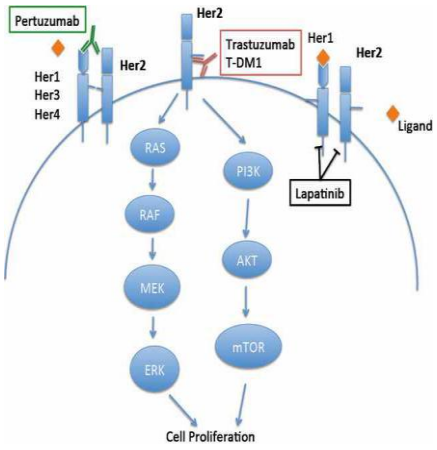

Figure 1. HER2 is a transmembrane receptor. Activation of HER2 results in cell signaling through the MAPK (RAS, RAF, MEK, and ERK) pathway and PAM (PI3K, Akt, mTOR) pathway, leading to cellular proliferation. Trastuzumab, T-DM1, pertuzumab and lapatinib bind to HER2 and result in inhibition of cell signaling. [4]

Trastuzumab, anti-HER2 humanized monoclonal antibody, binds to subdomain IV of the HER2 extracellular domain that results in blocking HER2 cleavage.[5] Adding trastuzumab to chemotherapy significantly improves progression-free and overall survival among patients with HER2-positive metastatic breast cancer.[6,7] Yet, HER2-positive metastatic breast cancer remains aggressive and progressive,[8] therefore, new targeted therapies for advanced disease are highly needed. New anti-HER2 therapies are being used,[9-12] among them pertuzumab, a humanized monoclonal antibody that binds the HER2 extracellular domain (subdomain II).[13]

Pertuzumab and trastuzumab, when given together, provide a dual blockade of HER2 signaling and result in greater anti-tumor activity because they bind to different HER2 domains in HER2-positive tumors.[14] Phase 2 studies have shown activity of this combination in patients with HER2-positive metastatic breast cancer.[15,16] furthermore, this activity was confirmed in patients with early breast cancer who received this combination as neo-adjuvant or adjuvant treatment.[17, 18]

Cleopatra study demonstrated that the first line combination of trastuzumab, pertuzumab, and docetaxel resulted in a median duration of progression-free survival and overall survival of 18.7 months and 57.1 months, respectively. It also showed that the objective response rate was 69.3% in the control group, as compared with 80.2% in the pertuzumab group (table1).[19]

In our institutional study, we evaluated pertuzumab and trastuzumab by assessing the clinical benefit of pertuzumab plus trastuzumab plus chemotherapy as first-line treatment for patients with HER2-positive metastatic breast cancer.

Table 1. Overall response (Cleopatra study)[19]

	T+D (N = 336)	P+T+D (N = 343)	
OR no. (%)	233 (69.3)	275 (80.2)	difference 10.8% (95% CI, 4.2 to 17.5; P=0.001)
CR no.(%)	14 (4.2)	19 (5.5)	
PR no.(%)	219 (65.2)	256 (74.6)	
SD no.(%)	70 (20.8)	50 (14.6)	
PD no (%)	28 (8.3)	13 (3.8)	
No assessment	5 (1.5)	5 (1.5)	

P, pertuzumab; T, trastuzumab; D, docetaxel. OR, objective response, CR, complete response,
PR, partial response, SD, stable disease, PD, progressive disease

Patients and methods:

Eligibility

Eligible patients had HER2-positive, advanced or metastatic breast cancer who had not received

chemotherapy or biologic therapy for their metastatic disease. An Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, measurable disease according to the (RECIST 1.1) for response evaluation in solid tumors,[20] a left ventricular ejection fraction (LVEF) within normal range; a life expectancy of at least 12 weeks; and adequate renal, hepatic, and hematologic function. Women with central nervous system (CNS) metastases were eligible if they were clinically stable for at least 3 months after the discontinuation of corticosteroid and anticonvulsant therapy. Women with heart disease were ineligible.

Study design and endpoints

This is a non-randomized, single-arm study. Patients received treatment at Albairouni university hospital and all patients provided informed consent. The endpoint was to determine the CBR and ORR. All our patients received Pertuzumab plus trastuzumab combining with either docetaxel or oral vinorelbine. Of note, adverse events were not assessed because two different cytotoxic regimens are used in combination with pertuzumab and trastuzumab.

Treatment plan

Combination Regimens:

Trastuzumab and pertuzumab (Herceptin, F. Hoffmann–La Roche/Genentech). Oral vinorelbine (Pierre Fabre Oncology). Docetaxel (generic). Single chemotherapy is used in this combination.

Patients received a loading dose of 8 mg/kg of trastuzumab, followed by a maintenance dose of 6 mg/kg every 3 weeks until disease progression, or the development of toxic effects that could not be effectively managed. Pertuzumab was given at a fixed loading dose of 840 mg, followed by 420 mg every 3 weeks until disease progression or the development of toxic effects that could not be effectively managed. Docetaxel was administered every 3 weeks at a starting dose of 75 mg/m2. Vinorelbine dosage was oral 60 mg/m² D1, D8, 3 week cycles. In the case of discontinuation of chemotherapy due to toxic effects, antibody therapy was continued until disease progression, the development of unacceptable toxic effects, withdrawal of consent, or drug shortage. All drugs were administered intravenously except vinorelbine that are given orally.

Efficacy assessments

Response was assessed routinely every 9 weeks and was defined according to RECIST criteria. Change in tumor burden was classified as complete response (CR), Partial response (PR), stable disease (SD) or progressive disease (PD). OR was CR or PR, while patients with CR, PR or SD were included in the CBR for at least 3 months.

HER2 detection

HER2-positive status is indicated by evidence of protein overexpression or gene amplification. Detecting HER2 was done by either Immunohistochemistry (IHC) or in situ hybridization (ISH). IHC describes overexpression of HER2 protein on the cell membrane on a scale of 0–3. HER2 is considered positive if grade 3+ staining intensity by IHC, or grade 2+ with gene amplification by fluorescence. ISH reveals the number of HER2 gene copies per cell and has been conducted with fluorescent, chromogenic, or silver detection probe (FISH, CISH, or SISH; respectively). A second probe labeling the centromeric region of chromosome 17 (CEP17) is often used to calculate the ratio of HER2/CEP17.

Results:

From June 2020 until December 2020, a total of 125 patients were enrolled at Albairouni university hospital (BUH), 60 patients were not evaluated due to drug shortage or disruption. Table 1 shows the baseline characteristics. The median patient age was 52 years. The majority of the patients had a good performance status. All patients were HER2-positive. The proportion of patients with visceral and non-visceral involvements was 80%, 20%, respectively. Patients received Pertuzumab plus trastuzumab plus chemotherapy (docetaxel or vinorelbine) until progression, as long as the drug is available.

Efficacy

65 patients were assessable for efficacy. The images were reviewed by our institution radiologists or outside facilities to confirm CR, PR, or SD, whereas determining the progression was based on investigator assessment. CBR and ORR were achieved in 95% and 81%, respectively (CR: 6%, PR: 75%, SD: 14%) of the study population. A progression was noted in 5% of patients.

Table 2. Baseline patient's characteristics

Registered Patients no.	120
Assessable Patients no.	65
Female sex no. (%)	65(100)
Age_ years Median Range	 52 (25-68)
ECOG performance status_ no. (%) 0 1	 43(66) 22 (34)
Hormonal receptors status_ no. (%) Positive for ER and/or PR Negative ER and PR	 36 (55.4) 29 (44.6)
Metastatic sites_ no. (%) Visceral Non-visceral	 52 (80) 13 (20)
Prior neo/adjuvant therapy no.(%) trastuzumab Anthracycline Taxane Hormone No treatment	 7 (10.7) 24 (37) 15 (23) 17 (26) 30 (46)
Current Chemotherapy regimens Taxane Vinorelbine oral	 31 34

Table 3. Overall Response.

Response	Patients N=65
CBR no. (%) OR no. (%) CR no. (%) PR no. (%) SD no. (%) PD no. (%)	 62 (95) 53 (81.4) 4 (6) 49 (75.4) 9 (14) 3 (5)

CBR, clinical benefit rate; CR, complete response; PR, partial response; SD, stable disease; PD, progression.

Table 4. Efficacy, subgroup. NVB vs. DCT

Trastuzumab + Pertuzumab	NVB o 60 mg/m² D1, D8 (n=34)	DCT 75-80 mg/m² D1 q3w (n=31)
CBR (%) OR (%) CR (%) PR (%) SD (%) PD (%)	94 79.38 8.8 70.58 14.7 5.8	96.77 83.8 3.2 80.6 12.9 3.2

CBR, clinical benefit rate; CR, complete response; PR, partial response; SD, stable disease; PD, progression.

Discussion:

The HER2–HER3 heterodimer is considered to be the most potent signaling pair, [21] driving cell proliferation in HER2-positive cancer.[22,23] Pertuzumab prevents HER2 dimerization and, as a consequence, inhibits HER2–HER3 signaling.[24] Adding pertuzumab to trastuzumab achieve a dual blockade of HER2 and greater anti-tumor activity in patients with HER2-positive metastatic breast cancer .[14-16]

Our institutional study, which is the first to evaluate this combination of pertuzumab and trastuzumab, confirmed the benefit of dual blockade of HER2. Our data demonstrate a 95% and 81% for CBR and ORR, respectively (Table 3). We found that the combination of the pertuzumab and trastuzumab with either docetaxel or Vinorelbine oral as first-line therapy showed significantly improvement of the clinical outcome in HER2-positive

metastatic breast cancer. Interestingly, it is also consistent with the Cleopatra trial.[19] Unfortunately; the survival data are not available.

Our findings confirm that targeting HER2-positive tumors with two anti-HER2 monoclonal antibodies that have complementary mechanisms of action results in a more comprehensive blockade of HER2 and highlights the correlated clinical importance.

This study has three weak points: First, drug disruption resulted in dismissing many patients. Second, the study design is a single group with small patient number. Third, we used two different cytotoxic regimens docetaxel or vinorelbine that prevent us from evaluating pertuzumab's adverse events. Indeed, previous studies demonstrated that vinorelbine + Trastuzumab have the best synergistic combination index.[25,26] In addition, oral vinorelbine plus trastuzumab is as effective as taxane plus trastuzumab in HER2+ MBC.[27] Furthermore, when dual blockade with trastuzumab and pertuzumab is used, possible single agents to combine are docetaxel, paclitaxel, or vinorelbine.[28] this leads to listing vinorelbine oral as a preferred choice in the recent publications on during COVID-19 Pandemic.[29] We also used oral vinorelbine because it is equivalent to its intravenous formulation,[30] In our study, patients had similar clinical benefit with first-line treatment of docetaxel or vinorelbine combined with trastuzumab and pertuzumab (table 4), and the benefit pronounced in patients who are either naïve or previously treated with trastuzumab was similar.

In conclusion, our findings confirm that dual targeting HER2-positive tumors with pertuzumab and trastuzumab has greater action and activity in MBC, in both naïve patients and who had received prior adjuvant or neo-adjuvant chemotherapy with trastuzumab. Additionally, oral vinorelbine should be highly considered for this combination.

Author's Disclosures

Author has no conflicts of interest to disclose.

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