تأثير معدل الـ +HER2 في فائدة التراستوزوماب عند مريضات سرطان الثدي المبكر

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الملخص

خلفية البحث وهدفه: مستقبل عامل النمو البطاني البشري (HER2) هو عامل تنبؤي عن مقدار الفائدة من العلاج المتمم بالتراستوزوماب (Trastuzumab هو علاج هدفي مضاد للـHER2) الذي يعدُّ العلاج الأمثل عند مريضات سرطان الثدي المبكر إيجابيات الـHER2 بعد انتهاء العلاج الكيميائي المتمم. هَدَفَتْ هذه الدراسة إلى تحديد تأثير ارتفاع مستوى إيجابية الـHER2 في الفائدة من العلاج المتمم بالتراستوزوماب، وفي الإنذار عند التشخيص.

مواد البحث وطرائقه: مريضات سرطان الثدي المبكر (إيجابيات الـHER، إيجابيات العقد اللمفية وسلبيات المستقبلات الهرمونية) اللواتي تلقّين التراستوزوماب بعد العلاج الكيميائي المتمم في مشفى البيروني الجامعي (157 مريضة). نمط المعالجة هو التراستوزوماب 8 ملغ/كغ وريدي جرعة تحميل تتبع بـ6 ملغ/كغ، يكرر كل 21 يوماً، مدة 6 أشهر. هذه الدراسة بذراعين اعتماداً على معدل إيجابية الـHER2. الذراع A (HER2FISH ≥ 4، عدد المرضى =91)، و الذراع B (HER2FISH < 4، عدد المرضى =66). الهدف الرئيسي هو تقييم البقيا الحرة دون مرض مدة ثلاث سنوات (Disease Free Survival)، وارتباطها بمعدل تضاعف الـHER2،

النتائج: كانت البقيا الحرة دون مرض، مدة ثلاث سنوات في الذراع A 75.8%، بينما كانت 77.2% في الذراع B (P = 0.31). كانت المرحلتان II وIII في الذراع A 32% و68% على التوالي، في حين كانت في الذراع B 27.27% و72.72% على التوالي. أمَّا بالنسبة إلى الدرجة الخلوية (I-II) و (III-IV): فبلغت في الذراع A 60.4% و 39.6% على التوالي، وفي الذراع B 68.18% و 31.81% على التوالي. كانت الفروق غير مهمّة إحصائياً.

الاستنتاج: أظهرت هذه الدراسة أن ارتفاع معدل تضاعف الـHER2 ليس له تأثير ملحوظ في الفائدة من العلاج المتمم بالتراستوزوماب، أو في الإنذار.

كلمات مفتاحية: سرطان الثدي المبكر، مستقبل عامل النمو (HER2)، التراستوزوماب.

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Impact of HER2+ Ratio on Efficacy of Trastuzumab in Early Breast Cancer

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Abstract

Background: Human epidermal growth factor receptor 2 (HER2) is a significant predictive factor for benefit from adjuvant trastuzumab (HER2-targeted therapy) which is considered the standard treatment for patients with HER2+ early breast cancer (EBC) after completion of adjuvant chemotherapy. We aimed to determine whether the high level of HER2 positivity would influence the outcome of adjuvant trastuzumab and the prognosis at diagnosis.

Patients and methods: 157 Patients with EBC (HER-2 positive, lymph node-positive, hormonal receptors negative) who received adjuvant chemotherapy and trastuzumab (8 mg/kg intravenously as a loading dose followed by 6 mg/kg every 3 weeks for 6 months) at Albairouni University Hospital. This is a single institute study with two arms based on HER2 positivity ratio. Group A (HER2 FISH ratio ≤ 4, n =91 patients), and group B (HER2 FISH ratio > 4, n =66 patients).The primary endpoint was 3-years disease free survival (DFS) in relation to HER2 FISH ratio.

Results: The 3-years DFS in the group A was 75.8%, while it was 77.2% in the group B (P = 0.31). Stage II and III in the group A were 32% and 68% respectively, while for the group B were 27.27% and 72.72% respectively. Grade (I-II) and (III-IV) for the group A were 60.4% and 39.6% respectively, while for the group B 68.18% and 31.81% respectively. Differences were not statistically significant.

Conclusion: the High degree of HER2 amplification (FISH ratio >4 vs. ≤4) has no significant influence on either outcome from adjuvant trastuzumab or prognosis in HER2+ EBC.

Key words: early breast cancer, HER2, trastuzumab.

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Introduction

Protein overexpression or gene amplification of human epidermal growth factor receptor 2 (HER2) occurs in approximately 20% of primary breast carcinomas and is associated with poor prognosis.[1-3] HER2 status is also a significant predictive factor for response to HER2-targeted therapies such as trastuzumab, pertuzumab, lapatinib or trastuzumab emtansine T-DM1 (Fig. 1).[4-8]

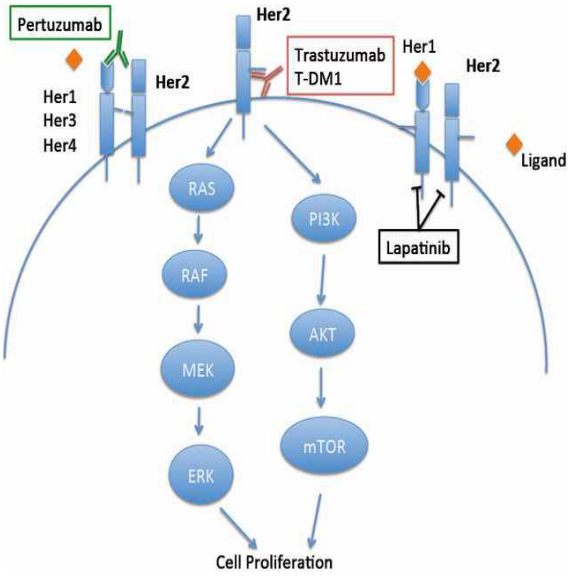

Figure 1. HER2 is a transmembrane receptor. Activation of HER2 results in cell signaling through the MAPK (RAS, RAF, MEK, and ERK) pathway and PAM (PI3K, Akt, mTOR) pathway, leading to cellular proliferation. Trastuzumab, T-DM1, pertuzumab and lapatinib bind to HER2 and result in inhibition of cell signaling. [8]

HER2-positive status is indicated by evidence of protein overexpression or gene amplification. Detecting HER2 may be 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.

Trastuzumab, a humanized monoclonal antibody targeting HER2, has demonstrated efficacy as a single agent or in combination with chemotherapy in patients with HER2-overexpressing metastatic breast cancer.[9-11] Furthermore, adjuvant treatments that include trastuzumab have become the standard of care for patients with HER2+ early breast cancer,[12-16] and HER2 testing is recommended at diagnosis of all breast cancers to determine potential eligibility for trastuzumab therapy.[17] The cutoff value of 2 was proposed in the American Society of Clinical Oncology (ASCO) and College of American Pathologists (CAP) guidelines 2013.[18]

Although there is a robust data regarding the association of HER2 overexpression and benefit of Trastuzumab, the relationship between the high level of HER2 positivity and the benefit from adjuvant treatment of trastuzumab is conflicting. HER2 positive breast cancers tend to grow more quickly than HER2 negative breast cancers. The higher the level of HER2, the more likely the cell is to grow and divide. Recent studies demonstrated that HER2+ tumors with the highest HER2 levels benefitted most from HER2 inhibitors.[19,20] Conversely, studies showed no association between the degree of HER2 amplification and the benefit from adjuvant trastuzumab (Fig. 2).[21,22]

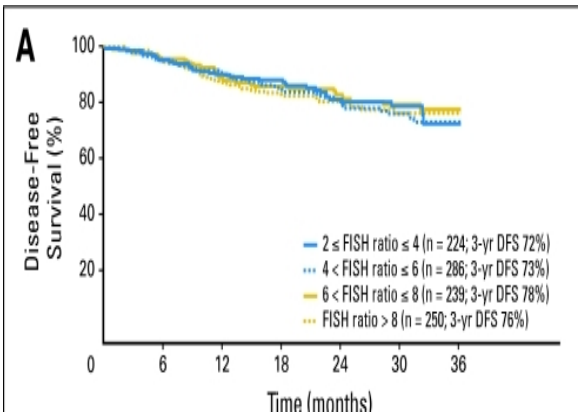

Fig. 2 HERA trial: Dowsett et al, Relationship between FISH Ratio with benefit from Trastuzumab [21]

We carried out this study to determine the impact of increased FISH ratio on disease-free survival (DFS) in patients with HER2+ early breast cancers treated with trastuzumab. We also analyzed the correlations between HER2 positivity level and prognosis at diagnosis including patient age, tumor's stage and histological grade.

Patients and methods

Patient populations

Early stage invasive breast cancer patients who treated with adjuvant trastuzumab at Albairouni University Hospital ABUH (aged ≤ 70 years with HER-2 positive, lymph node-positive, hormonal receptors negative, proved with histological invasive ductal or

lobular carcinoma at ABUH) were eligible for this study. Patients treated in adjuvant setting and completed surgery, radiotherapy and chemotherapy.

Study design and endpoints

This is a single institute study with two arms. Patients who treated with adjuvant trastuzumab between 2010 and 2012 were assigned according to HER2 amplification level to one of two groups: patients who had HER2 FISH ratio ≤4 (arm A = 91 patients), and patients who had HER2 FISH ratio > 4 (arm B = 66 patients). The primary endpoint of this trial was 3 years disease free survival (DFS). Secondary endpoints were to detect the relationship between the higher HER2 positivity ratio and median patient's age, tumor's stage and histological grade. Patients were monitored during the treatment and afterward every 3 months by the investigators for follow-up and no evidence of metastatic disease, with adequate bone marrow, liver, renal and cardiac functions. Data were conducted and analyzed after median 3-years of follow-up.

Treatment plan

Patients received 8 mg/kg trastuzumab intravenously as a loading dose followed by 6 mg/kg every 3 weeks for 6 months. The two groups received the same treatment of trastuzumab.

HER2 detection

The HER2 status (gene amplification) was determined using chromogenic in situ hybridization (CISH), or fluorescence in situ hybridization (FISH). FISH was performed either at ABUH our outside laboratories, and amplification ratio ≥2 indicating positive status.

Statistical analysis

DFS measured from date of surgery until occurrence of any of the following events: recurrence of breast cancer at any site; the development of ipsilateral or contralateral breast cancer; or death from any cause without documentation of a cancer related event. 3-years DFS was estimated with the Kaplan-Meier algorithm from the date of surgery, and CIs were estimated according to the Greenwood formula.[23,24] Data and Statistic analysis was carried out with Excel and SPSS (Statistical Package for Social Sciences) version 17. P value is considered significant if it is < 0.05.

Results

Patient characteristics

From 2010 until 2012, a total of 157 patients were treated and evaluated at ABUH. Table 1 shows the baseline characteristics. All patients were HER2 positive, axillary lymph-nodes positive and hormonal receptors negative. Among patients evaluated, 91 patients (60%) were HER2 FISH ratio ≤4 (arm A) while 66 patients (40%) patients were HER2 FISH ratio >4 (arm B). The whole population received adjuvant chemotherapy with trastuzumab. Chemotherapy regimens were anthracycline-taxane-based. Data on adjuvant treatment are reported in Table 2.

Table 1. Baseline patient characteristics

Charactaristic n = 157 pts	Group A (n = 91) FISH ratio ≤4 N (%)	Group B (n = 66) FISH ratio >4 N (%)
Age		
Median	46	45
Range	25-65	23-70
Menopausal		
Pre	31 (34)	23 (35)
Post	60 (66)	43 (65)
Histology		
Ductal	91 (100)	66 (100)
Lobular	0	0
Tumor Size		
T1	05(04.55)	13(19.69)
T2	59(53.69)	35(53.03)
T3	21(19.11)	15(22.72)
T4	06(05.46)	03(04.54)
Nodal status		
N0	0	0
N1	40(43.95)	27(40.90)
N2	35(38.46)	24(36.36)
N3	16(17.58)	15(22.27)
Clinical stage		
I	0	0
II	29(31.86)	18(27.27)
III	62(68.13)	48(72.72)
P value	0.57	
Grading		
G1-II	55(60.4)	45(68.18)
GIII-IV	36(39.6)	21(31.81)
P value	0.14	
Hormonal receptors		
Negative	91(100)	66(100)
Positive	0	0

Pts; patients

Table 2. Main treatment characteristics

Characterstics N = 157 pts	Group A N (%)	Group B N (%)
Surgery		
Conservative	9 (10)	7 (10.5)
Radical	82 (90)	59 (89.5)
Chemotherapy		
Anthracyclines-based	1	2
Anthra&Taxen-based	90	64
Non-Anthra &Taxen	0	0
Cycles of Chemo		
6	72 (79)	56 (85)
8	19 (21)	10 (15)
Radiotherapy		
Yes	91(100)	66(100)

Not	0	0
Hormonal therapy		
Yes	0	0
Not	91(100)	66(100)

Survival analyses

To determine whether increased HER2 positivity resulted in improved efficacy of trastuzumab in adjuvant setting, analyses were performed in two groups (A and B). The follow-up of the entire population was 36 months or until progression. Assessment and post-therapy follow-up were performed by investigators every 3 months according to NCCN Guidelines.[17]

DFS at 12, 24 and 36 months for the group A was 92.3%, 82.4% and 75.8% (95% CI, 65.1-82.9) respectively, while for the group B was 92.4%, 83.3% and 77.2% (95% CI, 64.5-83.9) respectively. Similar DFS was seen in the whole population (92.4%, 82.8% and 76.4% respectively), Table 3.

Kaplan-Meier curves showed that the 3-years DFS were 76.4%, 75.8%, and 77.2% in the whole population, the group A and the group B respectively, and these differences were statistically not significant ($P = 0.31$) (Fig. 3).

Secondary End Points

Patients' characteristics were listed in table 1 and analyzed to detect whether the degree of HER2 positivity has influence on prognosis including patient age, tumor's stage and histological grade at diagnosis.

Age ranged from 25 to 65 years with median age 46 years in the arm A, while the median age was 45 years with a range (23-70) in the arm B.

In the group A, stage II and III presented in 32% and 68% respectively, while in the group B Stage II and III were 27.27% and 72.72% respectively. The differences were statistically not significant ($P= 0.57$).

Grade (I-II) and (III-IV) for the arm A were 60.4% and 39.6% respectively, while for the arm B 68.18% and 31.81% respectively, with no statistically significant differences ($P = 0.14$).

Table 3. DFS by FISH ratio

Population/ treated with Trastuzumab	No. of pts	1 Year		2- Years		3-Year	
		DFS Events No. %	DFS %	DFS Events No. %	DFS %	DFS Events No. %	DFS % (95% CI)
FISH ratio ≥2	157	12 7.6	92.4	27 17.2	82.8	37 23.6	76.4 (66.5 to 82.1)
Group A 2≤FISHratio ≤4	91	7 7.7	92.3	16 17.6	82.4	22 24.2	75.8 (65.1 to 82.9)
Group B FISH ratio >4	66	5 7.6	92.4	11 16.7	83.3	15 22.7	77.2 (64.5 to 83.9)

DFS, Disease free survival;
FISH, fluorescence in situ hybridization.

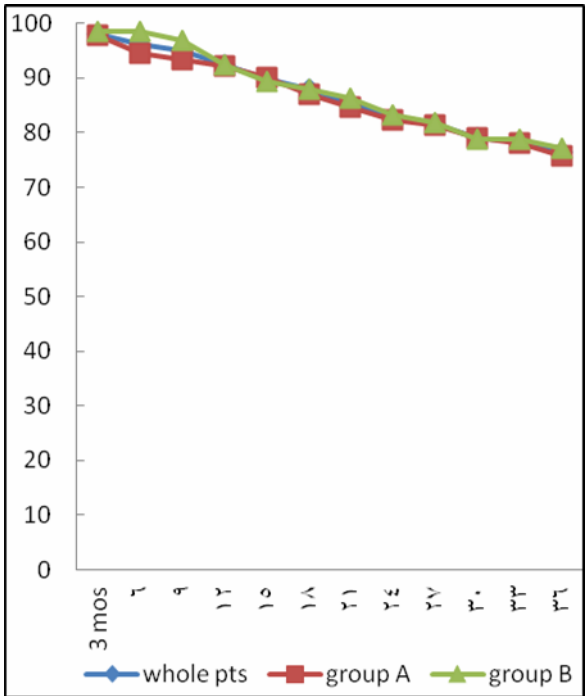

Figure 3. Saifo study, 3 years DFS according to HER2 FISH ratio

--- FISH ratio≥2(n = 157; 3-yr DFS 76.4%)
--- FISH ratio≤4 (n = 91; 3-yr DFS 75.8%)
--- FISH ratio>4 (n = 66; 3-yr DFS 77.2%)

Discussion

Several large randomized trials established trastuzumab as the standard treatment with chemotherapy in patients with early HER2-positive breast cancer.[12-16] Previous data from ABUH reported a similar conclusion and confirmed the impact of adjuvant trastuzumab.[25] The higher the level of HER2, the more likely the cell is to grow and divide. Although HER2 gene is a poor prognostic factor, it is considered a good predictive factor for treatment of trastuzumab as proposed by ASCO/CAP guidelines (the cutoff value of 2).

The relationship between the level of HER2 positivity and outcome of adjuvant treatment of trastuzumab is yet to be clearly demonstrated. The relatively high level of HER2 protein overexpression might conceivably lead to a higher benefit in such patients who treated with adjuvant trastuzumab. Recent studies showed that the HER2+ tumors with the highest HER2 levels benefitted most from HER2 inhibition.[19,20] On the other hand, studies including a popular one (HERA trial) indicated that the highest level of HER2 FISH ratio is not associated with a significant effect on either prognosis or benefit from trastuzumab in chemotherapy-treated population.[21,22]

This single institute study is to determine whether there is a significant relation between HER2 FISH positivity degree and DFS in early breast cancer treated with adjuvant trastuzumab after Chemotherapy at ABUH. We also studied the prognosis by analyzing patients' characteristics including age, tumor's stage and grade according to HER2 FISH ratio.

The subgroups amounted to less than 100 cases in each arm and these numbers are, however, modest to determine whether there is a significant interaction between HER2 degree and the benefit of treatment. Besides, the FISH analysis were conducted and collected from many laboratories.

In the present analyses, patients with HER2+ FISH ratio ≤ 4 achieved 3 years DFS of 75.8% (95% CI, 65.1-82.9) compared with 77.2% in those with HER+ FISH ratio >4 (95% CI, 64.5 to 83.9), with no marked difference in the benefit according to the degree of HER2 amplification ($P = 0.31$) (Fig. 3). In fact, there was no significant benefit found and these findings were consistent with analysis that was shown in the HERA trial (Fig. 2).[21]

Interestingly, our results suggested an increased stage III rate in relation to a higher level of HER2. 68.13% of patients with FISH ratio ≤ 4 were diagnosed with stage III, while 72.72% in those with HER2+ FISH ratio >4 (P = 0.57). In contrast, decreased High grade rate (III-IV) was noted in patients with HER2+ FISH ratio >4 (31.81%) versus (39.6%) in patients with FISH ratio ≤ 4, but not significant (P = 0.14). Besides, median age was similar in both arms.

In conclusion, our single institution study supports HERA trials findings and indicates that in HER2+ early breast cancer the high degree of HER2 amplification (FISH ratio >4 vs. ≤4) has no significant additional influence on either benefit from adjuvant trastuzumab or prognosis. Thus, demonstrating no predictive value of increased level of HER2 amplification for response to HER2-targeted therapies.

Author's Disclosures

Author has no conflicts of interest to disclose.

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