الفائدة السريرية من المشاركة الدوائية (Lapatinib + Capecitabine) عند مريضات سرطان الثدي الانتقالي +HER2

ماهر سيفو*

الملخص

خلفية البحث وهدفه: اللاباتينيب (Lapatinib) هو مثبط مزدوج للتيروزين كيناز، وهو حاصر لمستقبلي عامل النمو البطاني البشري (HER1,HER2). أظهرت الدراسات العالمية أن مشاركة اللاباتينيب مع الكابسيتابين (Capecitabine) لها فعالية جيدة عند مريضات سرطان الثدي الانتقالي إيجابيات الـ HER2 اللواتي عولجن سابقاً بكل من الإنتراسيكلين، والتاكسين، والتراستوزوماب. هذه الدراسة الأولى التي تجرى في مشفى البيروني الجامعي، و الهدف الرئيس هو تقييم الفائدة السريرية لهذه المشاركة الدوائية وآثارها الجانبية.

مواد البحث و طرائقه: أُدْرِجَتِ المريضات (إيجابيات الـ HER2، وسلبيات المستقبلات الهرمونية، المشخص لديهن سرطان ثدي انتقالي أو متقدم موضعياً، والناكسات على العلاج بكل من الإنتراسيكلين، والتاكسين، والتراستوزوماب). نمط المعالجة هو (لاباتينيب 1250 ملغ يومياً + كابسيتابين 2000 ملغ/م^2 من اليوم الأول وحتى اليوم 14، يكرر كل 21 يوماً). أعطيت المعالجة حتى تطور المرض. قُيِّمَتِ الفائدة السريرية (الاستجابة الكاملة، والاستجابة الجزئية، وثبات المرض) مدة لا تقل عن 3 أشهر.

النتائج: تم تقييم 60 مريضة، إذْ سجل معدل فائدة سريرية في 76% و 58.32% منهن، مدة 3 و 6 أشهر على التوالي. شوهد تطور المرض بعد أكثر من سنة عند 15 مريضة (25%). حدث استقرار المرض مدة تجاوزت السنتين عند مريض واحد. بلغ وسيط الوقت لتطور المرض (median time to progression) 8,1 أشهر [95%CI:6.5-11.2]. كانت أكثر التأثيرات الجانبية السريرية متوسطة الدرجة شيوعاً: غثيان 40%، إقياء 20%، إسهال 35%، متلازمة يد وقدم 41.7%، طفح 15%، و تعب 11.66%.

الاستنتاج: بيّنت هذه الدراسة وجود فائدة سريرية واضحة من المشاركة الدوائية (لاباتينيب+كابسيتابين) عند مريضات سرطان الثدي الانتقالي +HER2، سواء بنقائل حشوية أو دماغية، مع تأثيرات جانبية مقبولة.

كلمات مفتاحية: سرطان الثدي الانتقالي، مستقبل عامل النمو، Lapatinib، Capecitabine .

* مدرس - قسم الأورام - كلية الطب البشري - جامعة دمشق.

Improved outcome with Lapatinib plus Capecitabine In HER2 positive Metastatic Breast Cancer

Maher Saifo*

Abstract

Background &Objective: Lapatinib is a dual tyrosine kinase inhibitor blocking human epidermal growth factor receptors (HER1, HER2). Lapatinib in combination with Capecitabine has showed efficacy in HER2+ metastatic breast cancer (MBC) previously treated with Anthracycline, Taxens and Trastuzumab. This study is the first to evaluate the clinical benefit and safety of the combination of Lapatinib and Capecitabine in HER2+ MBC previously treated with anthracycline, taxane and trastuzumab, treated at Albairouni cancer center.

Methods & Material: Patients with HER2 Positive, hormonal receptors negative, locally advanced or metastatic breast cancer that had failed anthracycline, a taxane, and trastuzumab were enrolled. Patients received (lapatinib 1250 mg per day continuously plus capecitabine 2000 mg/m2 on days 1 through 14 of a 21-day cycle). Treatment was given until progression. The primary end point was the clinical benefit (complete response, partial response or stability) for at least 3 months.

Results: In the 60 evaluated patients, Clinical benefit rate was documented in 76% and 58.32% of the study population for 3 and 6 moths, respectively. Progression beyond one year was seen in 15 pts (25%). Interestingly, one patient achieved time to progression (TTP) >24 months. Median TTP was 8.1 months [95% CI: 6.5-11.2]. The most clinical side effects were mild: nausea (40%), vomiting (20%), diarrhea (35%), hand-foot syndrome (41.7%), rash (15%) and fatigue (11.66%).

Conclusion: The combination of Lapatinib and Capecitabine demonstrated a broad clinical benefit with acceptable safety profile in pretreated HER2+ metastatic breast cancer with either visceral or brain metastases.

Key words: metastatic breast cancer, HER2, lapatinib, capecitabine.

* Assist. Prof, Department of Oncology, Faculty of Medicine, Damascus University.

Introduction

Breast cancer is the second leading cause of death from cancer among women worldwide.[1] Approximately 20% of all breast cancer patients demonstrate an amplification or overexpression of Human epidermal growth factor receptor type2 (HER2), a tyrosine kinase tansmembrane receptor,[2] resulting in more aggressive phenotype and poorer prognosis.[3] Trastuzumab, a humanized monoclonal antibody that plays a key role in the treatment of metastatic and early stage HER2- positive breast cancer,[4-7] binds to the extracellular domain of HER2 protein,[8] mediating mitogenic signaling.[9] However, the cancer recurs after adjuvant therapy in some women,[6,7] and most patients with metastatic breast cancer eventually develops resistance to trastuzumab.[10,11] New therapies targeting HER2 are being developed,[11-13] among them lapatinib, a small molecule that targets tyrosine kinases of HER2 and Human epidermal growth factor type1 (HER1) receptors inside the cell, blocking downstream signaling events (Fig. 1).[14-16]

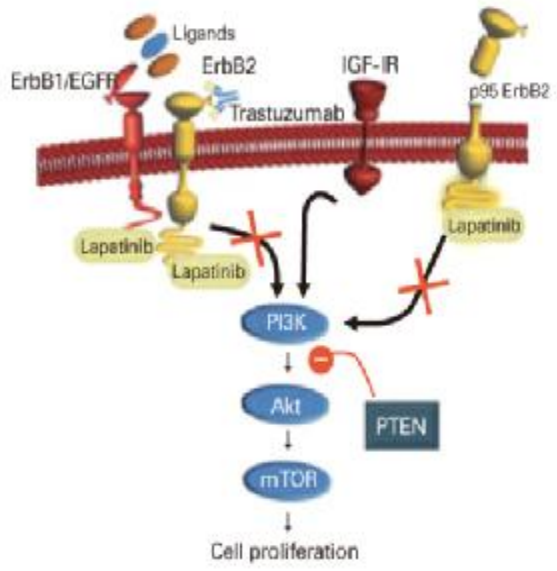

Figure 1. ErbB2 cellular signaling pathways and lapatinib mechanism of action. PI3K, phosphatidyl- inositol 3-kinase; IGFIR, insulin-like growth factor receptor; EGFR, epidermal growth factor receptor; mTOR, mammalian target of rapamycin; PTEN, phosphatase and tensin homolog.[14]

The clinical outcome and the safety profile of lapatinib in combination with capecitabine have been studied in women with HER-2 positive metastatic breast cancer progressed after Trastuzumab-based therapy (Table 1).[17,18]

In our institute, better outcome and less toxicity were noted. In this study, we aimed to: (1) determine the clinical benefit rate (CBR) and median time to progression (TTP), (2) assess the safety profile, and (3) compare our data with the international ones.

Table 1. Efficacy data of selected prospective study (Geyer et al)

End Point	L+C (N = 163)	C (N = 161)	Hazard Ratio (95% CI)	P Value
Median TTP- mo	8.4	4.4	0.49 (0.34-0.71)	< 0.001
Median PFS -mo	8.4	4.1	0.47 (0.33-0.67)	< 0.001
OR % (95% CI)				
CR no.(%)				0.09
PR no.(%)	22 (16-29)	14 (9-21)		
CB no.(%)	1 (<1)	0 (0)		
	35 (21)	23 (14)		
	44 (27)	29 (18)		

L, Lapatinib; C, Capecitabine; TTP, Time to progression; PFS, progression free survival; OR, overall response, CR, complete response, PR, partial response, CB, clinical benefit

Patients and methods

Eligibility

Eligible patients had HER2-positive, hormonal receptors negative, advanced or metastatic breast cancer that had progressed after treatment with regimens that included an anthracycline, a taxane, and trastuzumab. Women previously treated with capecitabine were ineligible; previous therapy with fluorouracil was permitted. 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,[19] 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 or conditions that could affect gastrointestinal absorption were ineligible.

Study design and endpoints

This study is a nonrandomized, single arm that sized for phase II clinical trial purposes. The primary endpoint was to determine the CBR. Secondary endpoints included median TTP and the safety profile.

Treatment plan

The combination regimen consisted of lapatinib at a dose of 1250 mg daily, 1 hour before or after breakfast, on a continuous basis, and capecitabine at a

dose of 2000 mg per square meter of body-surface area in two divided doses on days 1 through 14 of a 21-day cycle. Treatment continued until progression or unacceptable toxic effects.

Efficacy and toxicity assessments

Response was assessed every 3 months 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). Patients with CR, PR or SD were included in the CBR for at least 3 months. Secondary end points were median TTP and safety. Adverse events were assessed according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE v4.03).[20]

Statistical analysis

Response to treatment was evaluated using the Fisher's exact test. TTP was defined as the time from initiation of treatment until first evidence of radiographic progression or death due to breast cancer. Time to progression was estimated with the Kaplan-Meier algorithm. Statistic analysis was carried out with SPSS version 18.

HER2 detection

The HER2 status (gene amplification) was determined using chromogenic in situ hybridization (CISH), or fluorescence in situ hybridization (FISH) with an amplification ratio ≥2 indicating positive status.

Results

From January 2010 until December 2013, a total of 87 patients were enrolled at Albairouni university hospital, 27 patients were not evaluable for efficacy and toxicity analysis due to disruption. Table 2 shows the baseline characteristics. The median patient age was 51 years with 100% of patients aged between 28 and 60. The majority of the patients had a good performance status. All patients were HER2 positive and hormonal receptors negative. The proportion of patients with visceral, brain, and both involvements were 35%, 30%, and 23.33%, respectively. Patients who previously were treated with anthracycline, taxanes, and trastuzumab received lapatinib and capecitabine as second or third line.

Efficacy

60 patients were assessable for efficacy. The images were reviewed by our institution radiologists to confirm CR, PR, or SD, whereas determining the progression was based on investigator assessment. CBR for 3 months was achieved in 76.66% (CR: 0%, PR: 60%, SD: 16.66%) of the study population. A delay of progression of more than 6 months was noted in 58.33% (PR: 50%, SD: 8.33%) of patients. Progression beyond one year was in 15 pts (25%). Progression after two years was reported in one

Table 2. Baseline patient's characteristics

Registered Patients no.	87
Assessable Patients no.	60
Female sex no. (%)	60 (100)
Age_ years Median Range	 51 (28-60)
ECOG performance status_ no. (%) 0 1	 39 (65) 21 (35)
Hormonal receptors status_ no. (%) Positive for Estrogen and progesterone Negative	 0 (0) 60 (100)
Metastatic sites_ no. (%) Locally Advanced Visceral Brain only both	 7 (11.66) 21 (35) 18 (30) 14 (23.33)
Previous therapy_no. (%) Anthracycline Taxane Trastuzumab Hormone	 58 (97) 58(97) 60(100) 0
Study treatment setting_ no. (%) First line Second line Third line	 0 38 (63) 22 (37)
HER2 status by FISH_no. (%) Positive Negative	 60 (100) 0

Table 3. Efficacy results

		≥3 mo	≥6 mo	≥12 mo	>24 mo
Patients no	60				
CBR (%)		76.66	58.3	23.33	1.66
CR (%)		0	0	-	-
PR (%)		60	50	-	-
SD (%)		16.66	8.3	-	-
Median TTP mo (95% CI)	8.1 (6.5–11.2)				

CBR, clinical benefit rate; CR, complete response; PR, partial response; SD, stable disease; CI, confidence interval.

TTP, time to progression. patient (1.66%). Median TTP [95% CI] was 8.1 months [6.5-11.2] in the whole population. Median TTP appeared to be very similar to that reported in the international study (Table1), while the clinical benefit rate was higher in our study. Efficacy results are shown in Table 3.

Adverse events:

A total of 60 patients were assessable for non-hematological toxicity. Most adverse events were grade 1 and 2. Overall, the most common adverse events were nausea, vomiting, fatigue, diarrhea, the

hand-foot syndrome, and rash. No grade 4 was observed. Grade 3 diarrhea and the hand-foot syndrome occurred in three and two women, respectively. Two women of grade 2 rash were reported. Table 4 shows non-hematological adverse events. The incidence of any grade adverse events was lower than that in Geyer et al Study (Fig. 2).

Table 4. Non-hematological toxicity (National Cancer Institute-Common Terminology Criteria v4.03).

Event no. %	Any grade	Grade 3	Grade 4
Diarrhea	21 (35)	3 (5)	0
Hand-foot syndrome	25 (41.66)	2 (3.3)	0
rash	9 (15)	0	0
Fatigue	7 (11.66)	0	0
Nausea	24 (40)	0	0
Vomiting	12(20)	0	0

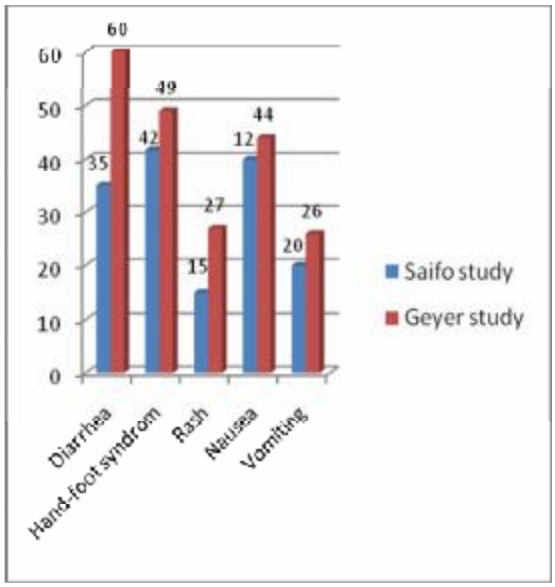

Figure 2. Most frequent adverse events. (All grades adverse events, %)

Discussion:

Treating cancer by blocking cell signals represent a successful strategy in the majority of human malignancies.[21] Many novel agents are discovered and approved, as evidenced by the approval of lapatinib (the dual HER1/HER2 kinase inhibitor).[15] Studies have reported that lapatinib plus capecitabine significantly improve the clinical outcome in HER2-positive metastatic breast cancer progressed after trastuzumab-based therapy.[17,18] In our institute, better outcome and less toxicity were observed. This single institute study is the first to evaluate the efficacy and toxicity of the combination of lapatinib with capecitabine at Albairouni University Hospital, and to compare our results with those observed in similar studies.[17,18] Interestingly, our data demonstrate a high CBR of 76.66% and 58.3% for 3 and 6 months, respectively (Table 3). We found better CBR compared to Geyer et al (27%). In fact, This study has two weak points: First, it is a nonrandomized clinical trial. Second, this study design draws conclusion from single group that sized for phase II clinical trial purposes, and no control exists. This fact precludes extensive comparisons with the results of previous randomized clinical trials. Nevertheless, we can state that our CBR of 58.3% is a promising result and is among the highest CBR reported until now. Indeed, these findings were consistent with our observation and expectation. In contrast, no obvious difference in median TTP was demonstrated in our study compared to Geyer trial (8.1 vs. 8.4 months). Although we did not find a difference in term of median TTP, our data indicate better CBR compared with Geyer et al. Observed toxicity was mild and manageable in our study. Table 4 summarizes non-hematological side effects and demonstrates that adverse events are minimum compared to Geyer study (Fig 2). Further, safety results should be highlighted. However, the most common adverse events were grade1-2: nausea, vomiting, fatigue, diarrhea, the hand-foot syndrome, and rash. Moreover, no grade 4 toxicity was observed.

In summary, This study supports our experience, observation and expectation. Given the least safety profile, the broad CBR reported make this combination of lapatinib and capecitabine a recommended option for the treatment of second or third line in HER2-positive advanced breast cancer patients with either visceral or brain metastases.

Author's Disclosures

Author has no conflicts of interest to disclose.

Reference

1. United Nations, Department of Economic and Social Affairs, Population Division (2013). UN World Population Prospects: The 2012 Revision. Accessed January 2015.
2. Wolff AC, Hammond ME, Schwartz JN, et al. (2007) J Clin Oncol, American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer. http://www.asco.org/guidelines/her2, 25, pp 118–145. 2007
3. Ross JS, Slodkowska EA, Symmans WF, et al. The HER-2 receptor and breast cancer: ten years of targeted anti-HER-2 therapy and personalized medicine. Oncologist. 2009;14:320–368.
4. Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonalantibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med 2001;344:783-92.
5. Vogel CL, Cobleigh MA, Tripathy D, et al. Efficacy and safety of trastuzumab as a single agent in first-line treatment ofHER2-overexpressing metastatic breast cancer. J Clin Oncol 2002;20:719-26.
6. Romond EH, Perez EA, Bryant J, et al.Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer.N Engl J Med 2005;353:1673-84.
7. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. N Engl J Med 2005;353:1659-72.
8. Molina M.A., Codony-Servat J., Albanell J., et al. Trastuzumab (herceptin), a humanized anti-Her2 receptor monoclonal antibody, inhibits basal and activated Her2 ectodomain cleavage in breast cancer cells. Cancer Res. 2001;61:4744–4749.
9. Junttila TT, Akita RW, Parsons K, et al. Ligand-independent HER2/HER3/PI3K complex is disrupted by trastuzumab and is effectively inhibited by the PI3K inhibitor GDC-0941. Cancer Cell 2009; 15:429-440
10. Montemurro F, Donadio M, Clavarezza M, et al. Outcome of patients with HER2-positive advanced breast cancer progressing during trastuzumab-based therapy. Oncologist 2006;11:318-24.
11. Baselga J, Swain SM. Novel anticancer targets: revisiting ERBB2 and discovering ERBB3. Nat Rev Cancer. 2009;9(7):463–475
12. Rabindran S.K., Discafani C.M., Rosfjord E.C., et al. Antitumor activity of HKI-272, an orally active, irreversible inhibitor of the HER-2 tyrosine kinase. Cancer Res. 2004;64:3958–3965. doi: 10.1158/0008-5472.CAN-03-2868.
13. Burris HA, 3rd, Rugo HS, Vukelja SJ, et al. Phase II study of the antibody drug conjugate trastuzumab-DM1 for the treatment of human epidermal growth factor receptor 2 (HER2)-positive breast cancer after prior HER2-directed therapy. J Clin Oncol 2011;29:398-405.
14. Vogel C, Chan A, Gril B, et al. Management of ErbB2-positive breast cancer: insights from preclinical and clinical studies with lapatinib. Jpn J Clin Oncol 2010;40:999–1013.
15. Moy B, Goss PE.Lapatinib: current status and future directions in breast cancer.Oncologist. 2006 Nov-Dec;11(10):1047-57. Review.
16. Xia W, Mullin RJ, Keith BR, et al. Anti-tumor activity of GW572016: a dual tyrosine kinase inhibitor blocks EGF activation of EGFR/erbB2 and downstream Erk1/2 and AKT pathways. Oncogene 2002;21 :6255-63.
17. Geyer CE, Forster J, Lindquist D, et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. N Engl J Med 2006;355:2733-43.
18. Cameron D, Casey M, Press M, et al. (2008) A phase III randomized comparison of lapatinib plus capecitabine versus capecitabine alone in
19. Therasse P, arbuck SG, new guidelines to evaluate the response to treatment in solid tumors Natl Cancer Inst 2009
20. http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf
21. Adjei AA, Hidalgo M. Treating Cancer by Blocking Cell Signals. Journal of Clinical Oncology, Vol 23, No 23 (August 10), 2005: pp 5279-5280 5279 DOI: 10.1200/JCO.2005.07.001.

تاريخ ورود البحث إلى مجلة جامعة دمشق 2015/2/11.
تاريخ قبوله للنشر 2015/4/6.