Clinical outcome of lapatinib and capecitabine in Her-2 +ve advanced/ metastatic breast cancer patients: A prospective study

Toson EA[1], Sharaf El Deen DA[1]

[1] Department of Clinical Oncology and Nuclear Medicine, Faculty of Medicine, Mansoura University, Egypt.

Abstract:

Background: The aim of this study was to evaluate the efficacy of lapatinib combined with capecitabine for patients with HER2 positive metastatic or unresectable locally advanced breast cancer who had previously been treated with anthracyclines, taxanes, and or trastuzumab.

Methods: Forty patients were enrolled. All patients received lapatinib 1250 mg once daily and capecitabine 2000 mg/m2/day, divided into 2 doses, on days 1-14, every 21 days. Tumor response was assessed by RECIST criteria version 1.1. Progression free survival (PFS) and overall survival (OS) were assessed using Kaplan- Meier method.

Results: Median age was (46 years), ranging (27-75). Four patients (10%) achieved complete response, 12 (30%) partial response, and 13 (32.5%) stable disease (SD). Overall response rate (ORR) was 40%. Clinical benefit rate (ORR+SD) was 72.5%. The median PFS was 12 months. Median OS was 22.6 months. Restricted performance status and three or more metastatic sites had significant impact on the OS and PFS. The protocol was well tolerated with manageable toxicity. Grade three hand and foot syndrome was observed in three cases and it was improved after reduction of capecitabine dose. Grade three neutropenia was detected in one case and was resolved with proper management.

Conclusion: The combination of lapatinib and capecitabine is relatively effective and well tolerated in improving PFS and OS in female patients with advanced and metastatic breast cancer after failure of other chemotherapeutic agents as anthracyclins, taxanes and trastuzumab.

Key Words: Clinical outcome, lapatinib and capecitabine, Her-2 +ve breast cancer.

Received: 1 February 2022
Accepted: 10 March 2022

Authors Information:
Eman Abdelkareem Toson
Clinical Oncology and Nuclear Medicine Department, Faculty of Medicine, Mansoura University. EGYPT
e-mail: Eman_toson@yahoo.com

Doaa Ali Sharaf El Deen
Clinical Oncology and Nuclear Medicine Department, Faculty of Medicine, Mansoura University. EGYPT
e-mail: Doalish@yahoo.com

Corresponding Author:
Clinical Oncology and Nuclear Medicine Department, Faculty of Medicine, Mansoura University. EGYPT
e-mail: Eman_toson@yahoo.com

Background:

Worldwide, breast cancer is the most common malignancy and cause of cancer-related death in women [1]. Despite improvements in early diagnosis and treatment, a significant portion of women relapse and die of metastatic disease.

About 20-25% of breast cancer patients over express human epidermal growth factor 2 (HER2). HER2-positive breast cancers show an aggressive behavior, poor response to chemotherapy and high incidence of local recurrence and distant metastasis [2].

Over the last decade, HER2 directed therapies, including trastuzumab, pertuzumab, lapatinib and trastuzumab emtansine (TDM) have been showed improved results in HER2 positive breast cancer [3-6].

Introduction of trastuzumab is associated with increase in overall survival (OS) and time to progression (PFS) when combined with chemotherapy in the first line treatment of metastatic breast cancer. However, resistance to anti-HER2 agents remains a challenge, highlighting a clinical need of novel therapies [7].

Lapatinib, is an orally bioavailable, small molecule tyrosine kinase inhibitor that targets both EGFR (epidermal growth facter receptors) and HER2 receptors. It blocks the phosphorylation of HER2 and AKT and extracellular signal regulated kinases ERK-1 and ERK-2[8,9] . Lapatinib was not associated with cross resistance with trastuzumab [10-12].

Several studies have demonstrated safety and efficacy of lapatinib combined with capecitabine for

patients with HER2 positive metastatic or locally advanced breast cancer whom had previously been treated with anthracyclines, taxanes, and or trastuzumab [13,14,15,16].

Based on the results of randomized phase III trial showing longer PFS in favor of Lapatinib, The American Food and Drug Administration (FDA) 2006 approved lapatinib and capecitabine combination as an effective regimen for treatment of advanced and metastatic Her2 positive breast cancer that had been treated previously by trastuzumab [4].

Other studies demonstrated that lapatinib was effective for treatment and prevention of brain metastasis in patients with metastatic HER 2 positive breast cancer [17,18] .

The present study was conducted to evaluate the efficacy and toxicity of lapatinib and capecitabine in metastatic or locally advanced HER2 positive breast cancer patients previously progressed on taxanes, anthracyclines and or trastuzumab

Patients and Methods:

This prospective study was performed at the department of Clinical Oncology and Nuclear Medicine, Mansoura University Hospital between May 2019 and May 2021. The study protocol was approved by the local ethics committee of Mansoura University (R⁄20.06.887). All enrolled patients were provided written informed consent.

Eligibility criteria:

Eligible participants were female ≥ 18 years, with histologically confirmed HER2-positive locally advanced or metastatic breast cancer. Eastern Cooperative Oncology Group (ECOG) performance status was 0-2, adequate bone marrow; cardiac, hepatic and renal functions were required. HER2 positive was defined as immunohistochemical staining of 3+ or 2+ with evidence of gene amplification in fluorescence in situ hybridization testing. All patients had failed taxanes, anthracyclines and or trastuzumab. Exclusion criteria were patients with uncontrolled symptomatic heart failure, left ventricular ejection fraction (LVEF) below institutional limit (55-70%), history of other malignancies, and patients received prior capecitabine.

Study protocol:

Eligible patients were assigned to receive lapatinib 1250 mg once daily and capecitabine 2000mg/m2/day, divided into 2 doses, on days 1-14, every 21 days. Dose reduction and delays (up to 2 weeks) for lapatinib and or capecitabine due to toxic events were allowed. Lapatinib was withheld for up to 14 days for grade II hematologic toxicity or any grade 3, 4 toxicity. Lapatinib was permanently discontinued if grade 3, 4 interstitial pneumonitis or cardiac dysfunction occurred. A dose reduction for lapatinib to 1000 mg was permitted. All patients received the treatment protocol until disease progression or unaccepted toxicity.

End points:

The primary end point was overall response (OAR). OAR was defined as the proportion of patients whose best response was either complete or partial. Tumor response was assessed using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.

The secondary end points include progression free survival (PFS) and overall survival (OS). PFS was the time elapsed from the date of initiation of treatment protocol to the date of first evidence of disease progression or death. OS was defined as the period from the first day of treatment until the date of last follow up or death.

Evaluation of safety

The tumor response was assessed using the RECIST criteria, version 1.1[19]. A patient was deemed to have had a complete response (CR) if there is no clinical and radiological evidence of the disease. Partial response (PR), At least a 30% decrease in the sum of diameters of target lesions. Stable disease (SD), neither sufficient decrease to qualify for PR nor sufficient increase to qualify for PD. Progressive Disease (PD), At least a 20% increase in the sum of diameters of target lesions. Assessment of the tumor responses were done radiologically as a baseline and every 12 weeks. Computed tomography and magnetic resonance imaging were the preferred methods of measuring the target lesions. Bone scans were indicated for patients with bone metastasis and were repeated every 24 weeks. Clinical and laboratory evaluation were done every three weeks. Clinical assessments included physical examination, vital signs, ECOG performance status, laboratory evaluation to evaluate the toxicity. Cardiac monitoring by echocardiography was performed every 12 weeks to evaluate left ventricular ejection fraction (LVEF).

Toxicities were evaluated according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (version 3). A grading scale was provided for each adverse event, from grade 1-4 corresponding to mild, moderate, severe, and life threatening. Treatment was continued until PD or unacceptable toxic effects. Cardiac event was defined as a drop in LVEF by 20% or more from the baseline. Lapatinib was discontinued in patients with symptomatic cardiac events.

Statistical analysis:

We calculated that a total of 40 time-to-progression events would be required to achieve 90% statistical power, with a one-sided and 5% type I error, to detect a 50% increase in the median time to progression. Statistical analysis of the data was made by using computer software (SPSS version 17.0). Kaplan Meier curves were used for OS and PFS. Response rate was expressed in percentage of evaluable patients. Log rank test is used to study the different prognostic factors. Statistical significance was considered when P value <0.05.

Results:

Forty patients met the eligibility criteria and they were enrolled in the study between May 2019 and May 2021. The median age was (46 years), ranging from (27-75). Nearly all patients (95%) had stage IV disease, most (80%) had extensive disease with visceral and / or non visceral metastasis and about 50% had an ECOG PS of 0 (table1).

Table1: Patient's data

	Number of patients (40)	(%)
Age Median 46 yrs Range (27-75)		
PS (ECOG)		
0	21	52.5
1	14	35
2	5	12.5
Menopausal status		
Premenopausal	23	57.5
postmenopausal	17	42.5
Hormone receptors		
ER,PR +ve	22	55
ER,PR –ve	14	35
ER+ve,PR-ve	4	10
Ki 67		
≥ 20%	27	67.5
< 20%	10	25
Unknown	3	7.5
Stage of the disease		
IIIB-IIIC	2	5
IV	38	95
Metastatic sites		
Liver	16	40
Brain	8	20
Bone	32	80
Lung	17	42.5
Others (local, axilla, skin)	6	15
Liver metastasis		
Yes	16	40
No	24	60
Brain metastasis		
Yes	8	20
No	32	80
No of metastatic sites		
≥ 3	18	45
< 3	22	55
Previous therapy		
Anthracyclin	28	70
Taxanes	32	80
Trastuzumab	19	47.5

PS (ECOG): Performance Status (Eastern Cooperative Oncology Group).

More than half of the patients (55%) were estrogen and progesterone receptor positive, 35% of them were negative for both and 10% were ER +ve and PR -ve. Nearly all patients (99%) had received chemotherapy for advanced or metastatic disease, 65% of them had received 2 chemotherapy regimens. 47.5% of patients had received prior trastuzumab (the median duration of trastuzumab therapy was 36 weeks), 80% of patients received taxanes. The most common non CNS metastatic sites were bone (80%), liver (40%), and lung (42.5%) with brain metastasis in 20% of the patients. The 8 patients were identified to have brain metastasis confirmed by magnetic resonance imaging or computed tomography scan before the initiation of lapatinib, capecitabine (relapsed after prior trastuzumab).

Survival results: (the primary end point is overall response)

At a median follow up of 15 months (range 4-39 months), there were 4 (10%) complete response, 12(30%) partial response, and 13(32.5%) stable disease (SD) resulting in an overall response rate (ORR) of 40%. Clinical benefit rate (ORR+SD) was 72.5% (table2).

Table 2: Treatment outcome

End point		
Median OS (months)	22.6	95% CI: 19.5-26.4
Median PFS (months)	12	95% CI: 10-14
	No=40	**%**
Overall response rate	16	40%
Complete response (CR)	4	10%
Partial response (PR)	12	30%
Stable disease (SD)	13	32%
Progressive disease (PD)	11	27.5%
Clinical benefit rate (ORR+SD)	29	72.5%

OS: Overall survival, PFS: progression frees survival and (ORR+SD): Overall response rate + stable disease.

Eleven patients (27.5%) had progressive disease (PD). In the overall survival analysis, fifteen (37.5%) patients died. The median progression free survival (PFS) was 12 months (95%CI: 10-14 months) (fig.1). The median overall survival (OS) was 18 months (95% CI: 14.5-21.5 months) (fig.2).

Adverse prognostic features that were significantly associated with poor OS included, poor performance status, presence of brain metastasis, liver metastasis, and three or more metastatic sites (p= <0.001), however , the age , hormonal status, ki 67, and menopausal status are independent predictor of OS (table 3). Better survival was noticed in patients received prior trastuzumab as compared with those not received it, with a median OS of 22month in trastuzumab group versus 9 months in those with no prior trastuzumab treatment (fig 3) The number of patients in the current study is small which might not be able for multivariate analysis.

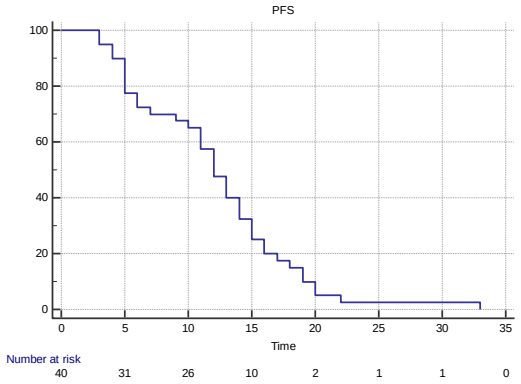

Figure 1: Progression free survival.

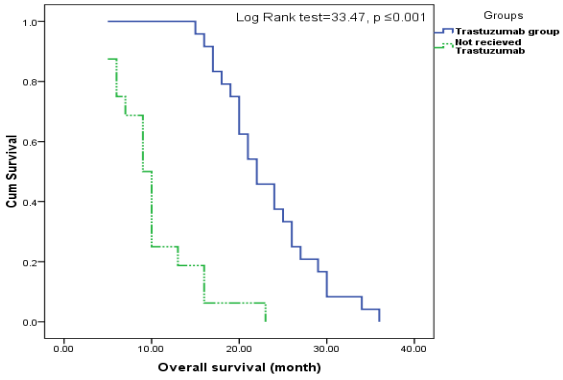

Figure 3: Overall survival for patients received prior Trastuzumab versus not received Trastuzumab.

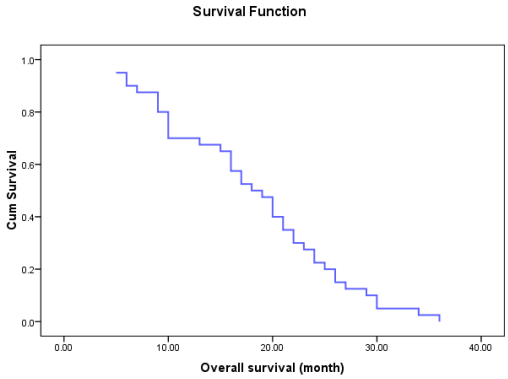

Figure 2: Overall survival

The results of log rank test and hazard ratios of all the studied risk factors was shown in (table 4), the median time to progression statistically significantly lower in patients with 3 or more metastatic sites and in patients with restricted performance status (1 or more) with hazard ratio of 3.74 and 5.36, respectively. In addition, presence of brain metastasis at presentation was barely significant (p=0.0515) with a median time to progression of 5 months Vs 13 months in those without brain metastasis. Similarly, presence of liver metastasis at presentation was barely significant (p=0.06) with a median time to progression of 5 months Vs 13 months.

Table3: Prognostic factors affecting overall survival (OS).

Risk factor	**N**	**Events N (%)**	**Median (95% CI)**	**Logrank test**	
				χ^2 (1)	**P value**
Age (years)				0.93	0.33
≤ 46	21	6 (28.6%)	- (-)		
>46	19	9 (47.4%)	22 (10 – 22)		
Brain Metastasis				21.68	<0.001
No	32	8 (25%)	- (-)		
Yes	8	7 (87.5%)	7 (5 – 17)		
Hormonal status				0.62	0.43
Positive	26	9 (34.6%)	- (-)		
Negative	14	6 (42.9%)	- (-)		
KI-67				7.70	0.006
< 20%	10	0 (0%)	- (-)		
≥ 20%	30	15 (50%)	22 (10 – 22)		
Liver Metastasis				28.25	<0.001
No	24	2 (8.3%)	- (-)		
Yes	16	13 (81.3%)	9 (6 – 17)		
Menopausal status				0.07	0.79
Premenopausal	23	8 (34.8%)	- (-)		
Postmenopausal	17	7 (41.2%)	- (-)		
Metastatic sites number				30.65	<0.001
< 3 sites	22	1 (4.6%)	- (-)		
≥ 3 sites	18	14 (77.8%)	10 (7 – 17)		
ECOG				27.79	<0.001
0	21	1 (4.8%)	- (-)		
≥ 1	19	14 (73.7%)	10 (7 – 17)		

CI= Confidence Interval. HR=Hazard Ratio. ECOG=Eastern Cooperative Oncology Group (A scale of performance status).

Table 4: Prognostic factors affecting progression free survival (PFS)

Risk factor	N	Median (95% CI)	Logrank test	
			χ^2 (1)	P value
Age (years)			0.93	0.33
> 46	19	13 (9 – 16)		
≤ 46	21	11 (6 – 14)		
Brain Metastasis			3.79	0.05
No	32	13 (11 – 15)		
Yes	8	5 (3 – 17)		
Hormonal status			0.02	0.89
Positive	26	12 (9 – 14)		
Negative	14	12 (4 – 15)		
KI-67			1.18	0.28
< 20%	10	13 (10 – 16)		
≥ 20%	30	11 (6 – 15)		
Liver Metastasis			3.51	0.06
No	24	13 (11 – 15)		
Yes	16	5 (4 – 14)		
Menopausal status			0.94	0.33
Postmenopausal	17	13 (5 – 16)		
Premenopausal	23	11 (6 – 14)		
Metastatic sites number			10.76	0.001
< 3 sites	22	14 (12 – 16)		
≥ 3 sites	18	6 (5 – 12)		
ECOG			16.25	<0.001
0	21	14 (12 – 18)		
≥ 1	19	6 (5 – 10)		

CI= Confidence Interval. HR=Hazard Ratio. ECOG=Eastern Cooperative Oncology Group (A scale of performance status).

Adverse events:

The combination therapy is generally well tolerated. The most common adverse events were hand and foot syndrome (52.5%), diarrhea (37.5%) and skin rash (42.5%). Most of these adverse events were mainly grade 1&2. One patient experienced grade 4 neutropenia which resolved after discontinuation of therapy and proper management. Seven patients developed hyperbilirubinemia, they had pre-existing liver metastasis, and one of them had grade three events. Three patients developed grade three hand and foot syndrome, they improved after reduction of capecitabine dose (table 5).

Table 5: Adverse events

Adverse events	Grade 1&2		Grade 3&4	
	No	%	No	%
Hand and foot syndrome	18	45	3	7.5
Diarrhea	15	37.5	0	0
Nausea	9	22.5	0	0
Vomiting	8	20	0	0
Stomatitis	8	20	0	0
Anorexia	6	15	0	0
Neutropenia	6	15	1	2.5
Dyspnea	2	5	0	0
Rash	16	40	0	0
Hyperbilirubinemia	6	15	1	2.5

Discussion:

The human epidermal growth factor receptor 2(HER2) is a strong mediator of cellular proliferation. Amplification of HER2 occurs in about 20% of breast cancers and is associated with poor outcome. Trastuzumab is a monoclonal antibody directed toward the extracellular domain of HER2 receptors, when combined with other chemotherapeutic agents, increase PFS and OS in advanced and metastatic HER2 positive breast cancer. Unfortunately, resistance to trastuzumab occurred [20,21].

In the present prospective study we evaluated safety and efficacy of lapatinib and capecitabine on patients with HER2 positive metastatic or advanced breast cancer who progressed on anthracyclines, taxanes and or trastuzumab. We observed a median PFS of 12 months and a median OS of 18 months. Our results are comparable to those reported by other registration trials who reported Median PFS of 8.4 months [4]. There are some differences between our patients and those in registration trials, our patients are slightly younger (median age 46 year), and those in registration trial were 54 year. This reflect Egyptian female develop breast cancer at younger age. Our results correlate with other data published by Latin American Cooperative Oncology Group who reported a median PFS 9 months and a median OS of 19.6 months [22]. Our study results was also comparable to another trial (Japanese trial) which yields a median time to progression of 36 weeks (95% CI 27.1- 48.0) [23].

Our research showed that the combination of lapatinib and capecitabine was effective and well tolerated representing an ORR of 40%, which correlate with that reported by Anatolian society of medical oncology, who reported an ORR of 33.4%, a median PFS of 7 months and a median OS of 15 months. We reported a better median PFS and OS owing to a relatively younger age, hormone receptor positive and relatively better performance status of our group of patients [24]. Other study resulted in an ORR of 49% (95% CI 34.8-63.4%) which are comparable to other published data [4,22,25,26].

The toxicity was manageable. Hand and foot syndrome was the most common adverse event representing 52.5%, most of them was of G1,2 (hand and foot syndrome in 45%, diarrhea in 37.5%), grade 3,4 toxicity occurred in 3 patients which was improved after dose reduction. Febrile neutropenia was uncommon (2.5%), it was corrected after discontinuation of therapy and proper management. These results were in accordance with those from previous reports [4,27,28,29].

Although anti Her2 are known to have a cardiotoxic effects, it was noticed that no cases of heart failure or decrease in LVEF. These results coincide with other data [25].

In the past years, new systemic treatment have become available for management of metastatic her 2 +ve breast cancer, the combination of pertuzumab and trastuzumab had been accepted as a first line treatment and produce improvement in PFS and OS. A second line treatment by trastuzumab emtansine has significantly improved results [22]. It was recommended by American society of clinical oncology clinical practice guidelines to continue HER2 blockade by lapatinib, capecitabine for patients with advanced disease who progressed after 2nd line pertuzumab and trastuzumab emtansine [29].

The limitations of this study were the small number of the enrolled cases. Also, after this research was conducted pertuzumab and T-DM1 had replaced lapitinib in the treatment protocol. We select patients with normal LVEF after treatment with anthracyclines and or trastuzumab and late cardiotoxic effects would not be followed because of relatively short period of follow up.

Conclusion:

In conclusion, the combination of lapatinib and capecitabine is relatively effective and well tolerated in improving TTP and OS in female patients with advanced and metastatic breast cancer after failure of other chemotherapeutic agents as anthracyclines, taxanes and trastuzumab. Further trials on larger populations with new novel therapy is recommended.

Financial support: The authors declares herby that the study did not receive any form of financial support.

Conflict of interest: No conflict of interest emerged during the implementation of this work. The paper had not been presented at any congress before.

Authors' contributions

ET carried out the design of the study, clinical work, performed the statistical analysis and participated in the sequence alignment and drafted the manuscript. DS conceived of the study, and participated in its design and coordination and helped to draft the manuscript. Both authors read and approved the final manuscript.

Acknowledgements

We thank Dr. Moneer Bahgat, Professor of Medicine, Mansoura University, Egypt, for his statistical assistance, as well as the all nursing team in Medical oncology and Nuclear medicine Department at Mansoura University Hospital for their support of this study.

References:

1. Slamon DJ, Godolphin W, Jones LA, et al. Studies of the HER-2/neu proto-oncogene in human breast and ovarian cancer. Science 1989, 244:707-712.
2. Eroglu Z, Tagawa T, Somlo G: Human epidermal growth factor receptor family-targeted therapies in the treatment of HER2-overexpressing breast cancer. Oncologist 2014, 19:135-150.
3. Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that over expresses HER2. N Engl J Med 2001, 344:783-792.
4. Geyer CE, Forster J, Lindquist D, et al. Lapatinib

plus capecitabine for HER2-positive advanced breast cancer. N Engl J Med 2006, 355:2733-2743.
5. Swain SM, Baselga J, Kim SB, et al. Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. N Engl J Med 2015, 372:724-734.
6. Verma S, Miles D, Gianni L, et al. Trastuzumab emtansine for HER2 positive advanced breast cancer. N Engl J Med 2012, 367:1783-1791.
7. Loibl S, Gianni L: HER2-positive breast cancer. Lancet 2017, 389:2415-2429.
8. Rusnak DW, Affleck K, Cockerill SG, et al. The characterization of novel, dual ErbB-2/EGFR, tyrosine kinase inhibitors: Potential therapy for cancer. Cancer Res 2001, 61:7196-7203.
9. 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, 21:6255-6263.
10. Rusnak DW, Lackey K, Affleck K, et al. The effects of the novel, reversible epidermal growth factor receptor/ErbB-2 tyrosine kinase inhibitor, GW2016, on the growth of human normal and tumor-derived cell lines in vitro and in vivo. Mol Cancer Ther 2001, 1:85-94.
11. Wood ER, Truesdale AT, McDonald OB, et al. A unique structure for epidermal growth factor receptor bound to GW572016 (lapatinib): relationships among protein conformation, inhibitor off-rate, and receptor activity in tumor cells. Cancer Res 2004, 64:6652-6659.
12. Konecny GE, Pegram MD, Venkatesan N, et al. Activity of the dual kinase inhibitor lapatinib (GW572016) against HER-2- overexpressing and trastuzumab-treated breast cancer cells. Cancer Res 2006, 66: 1630-1639.
13. Cameron D, Casey M, Press M, et al. A phase III randomized comparison of lapatinib plus capecitabine versus capecitabine alone in women with advanced breast cancer that has progressed on trastuzumab: updated efficacy and biomarker analyses. Breast Cancer Res Treat. 2008, 112:533–43.
14. Di Leo A, Gomez HL, Aziz Z, et al. Phase III, double-blind, randomized study comparing lapatinib plus paclitaxel with placebo plus paclitaxel as first-line treatment for metastatic breast cancer. J Clin Oncol. 2008, 26:5544–5552
15. National Comprehensive Cancer Network: NCCN Guidelines Version 1.2018: Breast Cancer2018. [https://www.nccn.org/store/login/login.aspx]
16. Larionov AA: Current therapies for human epidermal growth factor receptor 2-positive metastatic breast cancer patients. Front Oncol 2018, 8:89.
17. Lin NU, Di_eras V, Paul D, et al. Multicenter phase II study of lapatinib in patients with brain metastases from HER2-positive breast cancer. Clin Cancer Res 2009, 15(4):1452-1459.
18. Bachelot T, Romieu G, Campone M, et al. Lapatinib plus capecitabine in patients with previously untreated brain metastases from HER2-positive metastatic breast cancer (LANDSCAPE): a single-group phase 2 study. Lancet Oncol 2013, 14(1):64-71.
19. Eisenhauera EA, Therasseb P, Bogaertsc J, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1) European Journal of Cancer 2009, 45:228 – 247.
20. Dawood S, Broglio K, Buzdar AU, et al. Prognosis of women with metastatic breast cancer by HER2 status and trastuzumab treatment: an institutional-based review. J Clin Oncol 2010, 28:92–98.
21. 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.
22. Gómez, HL, Neciosup, S, Tosello, C, et al. A Phase II Randomized Study of Lapatinib Combined With Capecitabine, Vinorelbine, or Gemcitabine in Patients With HER2-Positive Metastatic Breast Cancer With Progression After a Taxane (Latin American Cooperative Oncology Group 0801 Study). Clinical Breast Cancer 2016, 16(1):38-44.
23. Iwata H, Fujii H, Masuda N, et al. Efficacy, safety, pharmacokinetics and biomarker findings in patients with HER2-positive advanced or metastatic breast cancer treated with lapatinib in combination with capecitabine: results from 51 Japanese patients treated in a clinical study. Breast cancer 2015, 22:192-200.
24. Cetin B, Benekli M, Dane F, et al. Lapatinib plus capecitabine for HER2-positive advanced-stage breast cancer: a multicenter study of Anatolian Society of Medical Oncology (ASMO). Journal of chemotherapy 2014, 26(5); 8: 300–305.
25. Xu BH, Jiang ZF, Chua D, et al. Lapatinib plus capecitabine in treating HER2-positive advanced breast cancer: efficacy, safety, and biomarker results from Chinese patients. Chin J Cancer 2011; 30:327-335.
26. Ro J, Park S, Kim S, et al. Clinical outcomes of HER2-positive metastatic breast cancer patients with brain metastasis treated with lapatinib and capecitabine: an open-label expanded access study in Korea. BMC Cancer 2012; 12:322.
27. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, et al. Trastuzumab after adjuvant chemotherapy in HER2-positivebreast cancer. N Engl J Med. 2005, 353:1659–1672.
28. Slamon D, Eiermann W, Robert N, et al. Adjuvant trastuzumab in HER2-positive breast cancer. N Engl J Med. 2011, 365(14):1273–1283.
29. Johnston S, Pippen J, Jr, Pivot X, et al. Lapatinib combined with letrozole vs. letrozole alone for front line postmenopausal hormone receptor positive (HRz) metastatic breast cancer. J Clin Oncol. 2009, 27: 5538–5546.