Efficacy and Safety of Lapatinib in Elderly Egyptian Patients with Her2 neu Positive Metastatic Breast Cancer

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Abstract:

Introduction: The efficacy and safety of the lapatinib based treatment remain challenging in elderly patients with her2neu positive metastatic breast cancer (MBC). Lapatinib exhibits a good overall tolerance, but no study has yet been dedicated to elderly women. The present study is a real world study that aimed to determine the efficacy and tolerability of the lapatinib based treatment in the first line setting in Egyptian patients with HER2neu positive MBC who cannot get access to trastuzumab.

Patients and Methods: In this retrospective study, 60 elderly patients (≥ 65 years) with her2neu positive MBC and treatment naïve were included.

All patients were treated with the combination of lapatinib (1,250 mg/day, continuously) and chemotherapy (either capecitabine 2,000 mg/m2 on days 1–14 of a 21-day cycle or weekly taxol 80 mg/m2), or lapatinib (1,250 mg/day, continuously) and hormonal treatment. Data on demographics, clinical outcome, and toxicity were collected form the patients' medical records for descriptive analyses.

Results: The median follow-up was 23.5 months (range 11–36 months). Most of the patients were hormone receptor positive (70%). About 28% of the patients had multiple sites of metastasis while 16 patients (26.7%) had bone only metastasis and 11 patients (18.3%) had lung only metastasis. Most of our patients (63.3%) had no associated comorbidities. An overall response rate of 61.7% was achieved, including 2 complete responses (3.3%), and 13 partial responses (21.7%). Median progression-free survival was 15.9 months (95% confidence interval (CI) 13.56- 18.33), and the median overall survival was 19.9 months (95% CI 17.8-21.9). Most common grade 1-2 side effects were diarrhea (43.3%), followed by hand-foot syndrome (35%), and skin rash (13.3%). Grade 3–4 toxicities were identified as hand-foot syndrome (10%), diarrhea (6.6%). There were no symptomatic cardiac events. Tolerability data show that 45% of patients needed a lapatinib dose reduction, and 30% a treatment interruption due to toxicity, while treatment discontinuation occurred in 18.3% of the cases.

Conclusion: Lapatinib based therapy in elderly patients with her2neu positive MBC was effective. However, it was not well tolerated especially when combined with chemotherapy.

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Introduction:

Human epidermal growth factor receptor 2 (HER2neu) positive is about 15–20% of all breast cancers and is slightly less in elderly patients (abut 10-1%). HER2neu positive breast cancer was associated with poorer disease free and overall survival (1). The breast cancer incidence is 2–3 times more in female aged ≥ 65 years than in the others and is associated with 3 to 4-fold higher in mortality rate (2).

The use of anti-HER2 therapies, especially when combined with chemotherapy, have dramatically improved survival (3).

Lapatinib is a small molecule tyrosine kinase inhibitor that targets both HER2 and EGFR1. Multiples studies demonstrated lapatinib efficacy in combination with chemotherapy, endocrine therapy, or trastuzumab also exhibits a good overall tolerance, but no study has been dedicated to elderly women (4).

Unfortunately, older patients remain under-represented in clinical trials and patients included in

these studies usually do not represent older patients in the general population (5).

Limited data is available on lapatinib use in older patients with BC. A series of 26 cases above age 65 showed a median progression-free survival (PFS) of seven months with lapatinib and capecitabine (close to the 8.4 months improvement in time to progression obtained in the registration trial) (6). Though in this series, lapatinib was overall reasonably well tolerated with only two interruptions due to AEs and only one treatment discontinuation due to adverse event, this has not been the case in the adjuvant setting in which tolerability and treatment completion rates are major concerns (7).

Patients and Methods:

Metastatic breast cancer HER2neu elderly women aged 65 years or more and treatment naïve who presented to Mansoura University Hospital from Jan 2016 to Dec 2017 and cannot get access to trastuzumab, were eligible for this retrospective study. All patients were required to have adequate performance status (Eastern Cooperative Oncology Group performance status); adequate hematologic; renal and liver functions.

All patients were treated with the combination of lapatinib (1,250 mg/day, continuously) and chemotherapy (either capecitabine 2,000 mg/m2 on days 1–14 of a 21-day cycle or weekly paclitaxel 80 mg/m2), or lapatinib (1,250 mg/day, continuously) and hormonal treatment.

Data on demographics, clinical outcome, and toxicity were collected form the patients' medical records for descriptive analyses

Assessment of efficacy and safety:

Disease progression was assessed using the modified Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Patient follow up generally consisted of regular physical examination and laboratory assessment (hematologic and serum chemical measurements), every 4–6 weeks, left ventricular ejection fraction (LVEF) evaluation and computed tomography (CT) scans were performed according to the local standard every 12–18 weeks. Patients with complete remission (CR), partial remission (PR), or stable disease (SD) were considered as responders. Patients were monitored for side effect according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (version 4.0).

Statistical analysis:

Data were analyzed using the Statistical Package of Social Science (SPSS) program for Windows (Standard version 24). The normality of data was first tested with one-sample Kolmogorov-Smirnov test.

Qualitative data were described using number and percent while continuous variables were presented as mean ± SD (standard deviation).

Kaplan- Meier test was used for survival analysis and statistical significance of differences among curves was determined by Log-Rank test. Cox regression model was used to predict the most significant determinants for mortality.

Level of significance:

For all above mentioned statistical tests done, the threshold of significance is fixed at 5% level. Results was considered significant when $p \leq 0.05$.

The smaller the p-value obtained, the more significant are the results.

Results:

60 patients, who cannot get access to trastuzumab, had received a lapatinib based regimen after being diagnosed with de-novo Her-2 positive MBC were retrospectively analyzed in the present study. The patient demographics and baseline clinical characteristics are summarized in Table (1).

Table (1): Patients characteristics among the studied group

Patients' characteristics	Study group (n=60)
Age/years	
Mean ± SD	**68.53±3.03**
Performance status	
0-1	38 (63.3%)
2	22 (36.7%)
Hormonal status	
Positive	42 (70.0%)
Negative	18 (30.0%)
Site of metastasis	
Bone	16 (26.7%)
Liver	10 (16.7%)
Lung	11 (18.3%)
Brain	6 (10.0%)
Multiple sites	17 (28.3%)
Associated co morbidity	
No	38 (63.3%)
Ischemic heart disease	8 (13.3%)
Diabetes	7 (11.7%)
Liver impairment	7 (11.7%)
Response	
Complete response	2 (3.3%)
Partial response	13 (21.7%)
Stationary disease	22 (36.7%)
Progressive disease	23 (38.3%)

The mean age was 68.5 years. 38 patients (63.3%) have a performance status from 0 to1 and 22 patients (36.7%) with score 2 performance status. The hormone receptor status was positive in 42 (70%) and negative in 18 (30%) cases. The multiple metastatic sites were common in 17(28.3%) patients, followed by bone (26.7%) then lung (18.3%), then liver in 16.7% and

lastly brain metastatic in 10.0% of the cases. Most of our patients (38 cases) had no comorbidities. Only 8 patients (13.3%) had IHD, 7 cases (11.7%) with diabetes mellitus and 7 cases (11.7%) with liver impairment.

An overall response rate of 61.7% was achieved, including 2 complete responses (3.3%), and 13 partial responses (21.7%), while SD in 22 cases (36.7%) and PD in 23 cases (38.3%).

Table (2) illustrates the overall survival which was 19.9 months (95% CI 17.8-21.9). The most effective parameters which has statistically significant effect on OAS were the performance status, hormonal status, site of metastases and finally the response to treatment which was demonstrated in (Fig 1), but the association of comorbidities has no statistically significant effect on OAS.

Median progression-free survival was 15.9 months (95% confidence interval (CI) 13.56- 18.33) which was represented in table (3). The factors which had statistically significant effect on PFS were performance status, hormonal status, site of metastases and response to treatment which are represented in Fig (2).

The adverse effect was represented in table (4); most common side effect was grade 1 and 2 diarrhea (43.3%) followed by hand foot syndrome (35%) and rash (13.3 %). Grade 3 and 4 hand and foot syndrome was noticed in 6 patients, grade 3 and 4 diarrhea in only 4 patients (6.6%) and grade 3 and 4 rash in 2 patients (3.3%). Lt ventricular affection was noticed in 7 cases (11.6%).

Table (2): Predictors for overall survival

Patients' characteristics	**Overall survival/ month**				
	Mean Survival time	**Std. Error**	**95% CI**	**Log rank test**	**P- value**
Performance status					
0-1	22.63	1.34	20.01-25.25	16.78	≤0.001*
2	15.18	1.11	13.01-17.35		
Hormonal status					
Positive	22.14	1.29	19.60-24.68	18.07	≤0.001*
Negative	14.67	0.936	12.83-16.50		
Site of metastasis					
Bone	30.31	1.61	27.14-33.47	43.67	≤0.001*
Liver	17.70	1.55	14.66-20.73		
Lung	17.45	1.71	14.08-20.82		
Brain	13.33	1.22	10.92-15.74		
Multiple sites	15.29	0.821	13.68-16.90		
Associated co morbidity					
Yes	18.63	1.69	15.32-21.95	0.826	0.364
No	20.63	1.33	18.02-23.23		
Response					
CR	36.00	0.00	36.00-36.00	71.51	≤0.001*
PR	30.46	1.83	26.87-34.05		
SD	19.27	0.655	17.98-20.56		
PD	13.13	0.468	12.21-14.05		
Overall survival (month)	19.90	1.04	17.8-21.9	-	-

Table (3): Predictors for progression free survival

Patients' characteristics	Progression free survival (month)				
	Mean Survival time	**Std. Error**	**95% CI**	**Log rank test**	**P- value**
Performance status					
0-1	19.42	1.62	16.23-22.61	22.35	≤0.001*
2	9.95	0.749	8.48-11.42		
Hormonal status					
Positive	18.45	1.55	15.41-21.49	14.87	≤0.001*
Negative	10.11	0.84	8.45-11.765		
Site of metastasis					
Bone	29.12	1.87	25.44-32.80	50.75	≤0.001*
Liver	13.40	1.43	10.57-16.22		
Lung	12.36	1.13	10.13-14.59		
Brain	10.00	0.894	8.24-11.75		
Multiple sites	9.47	0.665	8.16-10.77		
Associated co morbidity					
Yes	13.90	1.77	10.42-17.39	1.82	0.176
No	17.13	1.60	13.98-20.27		
Response					
CR	36.00	0.00	36.00-36.00	77.01	≤0.001*
PR	27.69	2.19	23.38-31.99		
SD	15.50	0.957	13.62-17.37		
PD	8.00	0.00	8.00-8.00		
PFS (month)	15.95	1.21	13.56- 18.33	0.964	0.326

Table (4): Lapatinib related adverse effects

Toxicity	Grade 1/2 60 pts (%)	Grade 3/4 60 pts (%)
Diarrhea	26 (43.3)	4 (6.7)
Rash	8 (13.3)	2 (3.3)
Hand foot syndrome	21 (35)	6 (10)
Left ventricular affection	7 (11.7)	0

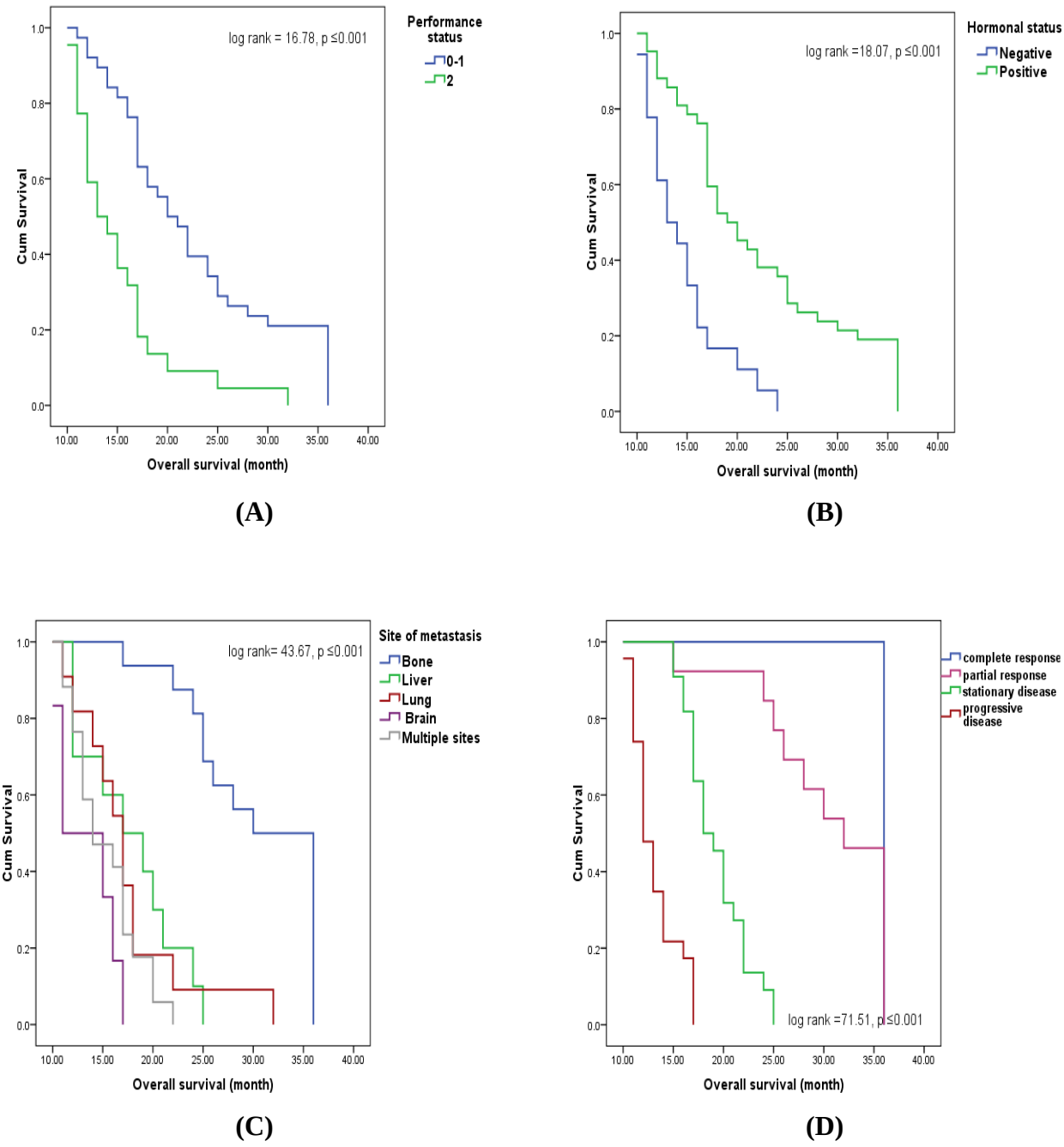

Fig1: Kaplan-Meier analysis of overall survival (A: in relation to the performance status, B: in relation to hormonal status, C: in relation to site of metastases and D: in relation to treatment response)

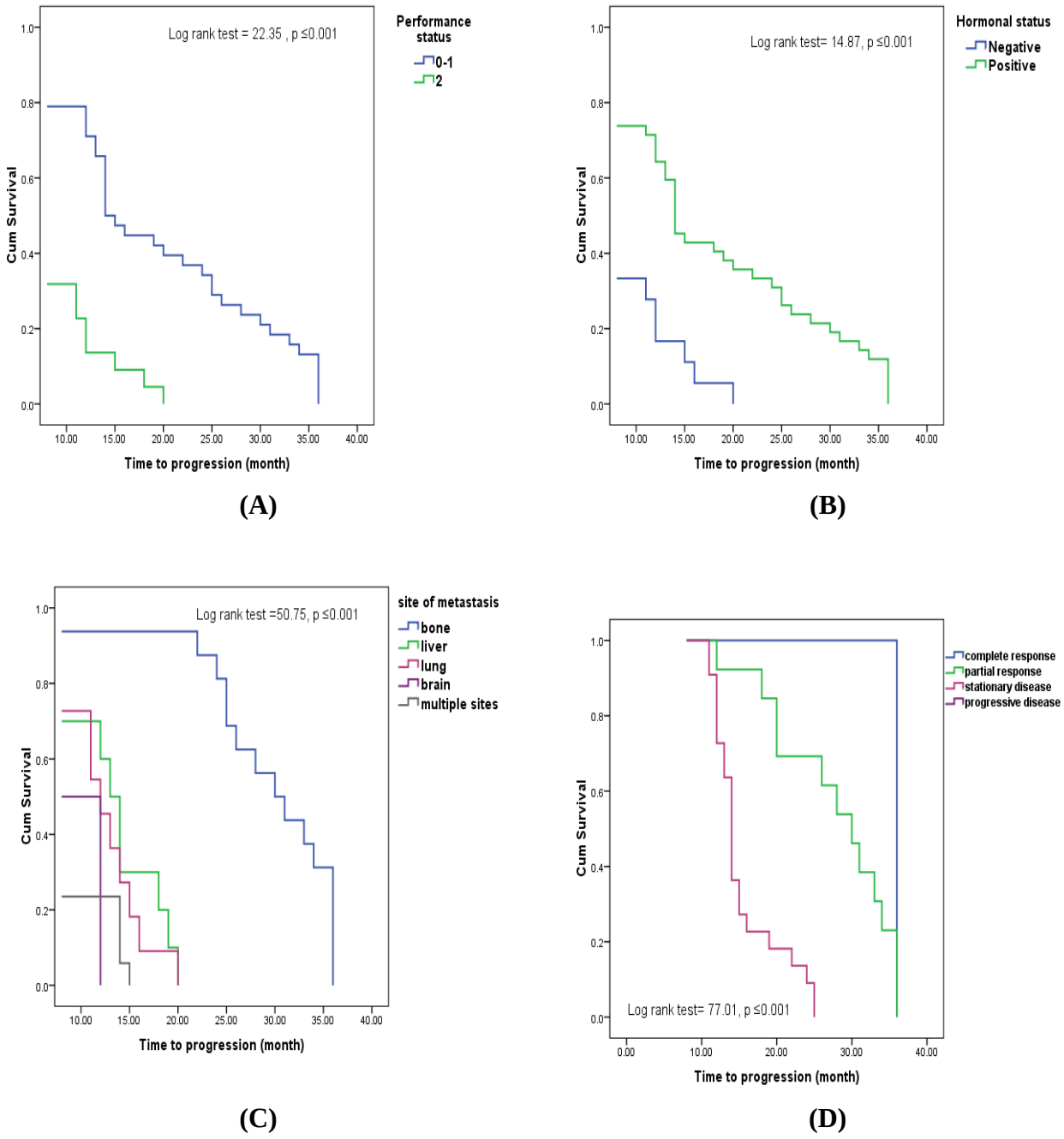

Fig 2: Kaplan-Meier analysis of progression free survival (A: in relation to the performance status, B: in relation to hormonal status, C: in relation to site of metastases and D: in relation to treatment response)

Discussion:

Anti HER2 agents are supposed to be used soon after the diagnosis of HER2+ MBC. The agents targeting HER2 and its pathway are associated with notable clinical benefits in patients having received treatment with trastuzumab. In 2010, Lapatinib was approved for use in combination with capecitabine in patients with HER2 positive MBC who had received prior treatment, including treatment with an anthracycline, taxanes and trastuzumab (8).

In this study, 60 elderly patients (≥ 65 years) with her2neu positive MBC and treatment naïve were included. 18 patients were treated with the combination of lapatinib (1,250 mg/day, continuously) and chemotherapy (either capecitabine 2,000 mg/m2 on

days 1–14 of a 21-day cycle or weekly taxol 80 mg/m2), in hormonal receptors negative or lapatinib (1,250 mg/day, continuously) and hormonal treatment in 42 cases with positive hormonal receptors as it's the first line setting in Egyptian patients with HER2-neu positive MBC who cannot get access to trastuzumab aiming to assess its efficacy and tolerability .

Freyer et al., reported that elderly patients were more likely to present with initial metastasis (> 75 years, 52%; 65–74 years, 39%; p< 0.0001), while in this study, the mean of age ± SD was 65.5±3.03 and the incidence of an ECOG PS of 0 in patients aged 64 to 75 years was more frequent than in those aged > 75 years (25% vs. 9%, p< 0.0001) in comparison to this study, ECOG PS of 0-1 was 63.3% and 2 was 36.7% as patients included to tolerated the treatment also age has already been reported to be a significant factor related to treatment selection in elderly patients with MBC (9,10).

Also, in a Turkish study, which included 26 patients with the patient's criteria were mostly similar to our study. As regarding the response, there were 1 (3.4%) with CR, 8 (30.8%) with PR, 10 (38.5%) with stable disease (SD), and 7 (26.9%) with progressive disease (PD) (5) while in our study, overall response rate of 61.7% was achieved, including 2 CR (3.3%), and 13 PR (21.7%), while SD in 22 cases (36.7%) and PD in 23 cases (38.3%).

In the Lapatinib Expanded Access Program (LEAP), median PFS and OS were reported to be 21.1 (95% CI 20.1–22.3) and 39.6 (95% CI 37.7–40.7) weeks, respectively (11) and In another study (EGF100151), median time to progression as assessed by the independent review committee was documented as 27.1 weeks (6.2 months), and median OS was 67.7 weeks (15.6 months) (12) while in our study median PFS was 15.9 months (95% confidence interval (CI) 13.56-18.33), and the median OAS was 19.9 months (95% CI 17.8-21.9).

XINYU et al., reported that Lapatinib based combination treatment was effective and well tolerated, with a median PFS of 5.8 months, a median OS of 21.5 months, an ORR of 21.7%, a DCR of 87.0% and limited side effects (13).

When BC has progressed on first line trastuzumab and chemotherapy, combination of the HER2 (TKI) lapatinib with capecitabine prolongs time to progression vs. capecitabine alone (14).

Similarly, the EMILIA trial (15) randomized patients with HER+ MBC who had been pretreated with trastuzumab and taxane to receive trastuzumab emtansine (T DM1) or lapatinib plus capecitabine. The results revealed a median PFS of 9.6 months with T DM1, compared with 6.4 months with lapatinib plus capecitabine (HR=0.65; 95% CI: 0.55 0.77; P<0.001). Trastuzumab plus chemotherapy or endocrine therapy is commonly used at present as first line treatment for HER2+ MBC. However, lapatinib combined with chemotherapy may be another option for trastuzumab pretreated patients, since T DM1 was not approved until January 2020 in China.

Capecitabine in combination with lapatinib is an acceptable treatment option for patients, since the agents may be taken orally at home, are associated with limited side effects and contributing to an optimal quality of life for these patients. In addition, the pharmacological mechanisms underlying the positive interaction between lapatinib and capecitabine were investigated in human breast cancer models, and it was observed that lapatinib clearly down regulated thymidylate synthase (TS) activity, thereby improving the efficacy of capecitabine, and that capecitabine optimized the down regulation of p AKT and p P42/44 expression by lapatinib. Specifically, lapatinib and capecitabine modulated each other's molecular determinants of response, and concomitant dosing appeared to be the optimal method for combining these agents, which suggested that the association between lapatinib and capecitabine has the potential to overcome breast cancer resistance associated with TS overexpression (16).

A study from Turkey (7) also demonstrated that lapatinib plus capecitabine treatment conferred a significant survival benefit to patients with brain metastasis from breast cancer, as compared with trastuzumab based treatment. The present analysis confirmed the benefits of lapatinib in patients with brain metastases from HER2+ breast cancer.

In the MA.31 trial, PFS was shorter for lapatinib plus taxane compared with trastuzumab plus taxane administered as first-line therapy of metastatic breast cancer (9.0 ms vs. 11.3 ms; HR 1.37 [95% CI 1.13–1.65]; P = 0.001) (17). Although Lapatinib has a different mechanism of inhibition on HER2 and EGFR signaling compared with trastuzumab. Preclinical evidence suggests non cross resistance to trastuzumab and lapatinib (18).

The only influence of age seems on risk of diarrhea: in a combined analysis of 11 trials, grade 3 events were more frequent in patients aged over 70 (33% vs. 19%) (19). However, enthusiasm for lapatinib decreased following the head-to-head comparison suggesting inferiority to trastuzumab based treatment (20) and the introduction of new drugs. The difficulty in managing lapatinib side effects may also have contributed to reduced usage.

The Chines trial, the lapatinib based combination treatment was generally well tolerated. The most common lapatinib related AEs were diarrhea, rash and hand foot syndrome. Diarrhea was recorded in 16 patients (4 cases of grade 1, 11 cases of grade 2 and 1 case of grade 3). Rash was recorded in 9 patients (6 cases of grade 1 and 3 cases of grade 2). Hand foot syndrome was recorded in 4 patients (2 cases of grade 1, 1 case of grade 2 and 1 case of grade 3). There was no episode of febrile neutropenia or symptomatic cardiac events. The dose of lapatinib was reduced in 14 patients, of whom 12 had diarrhea and 2 had hand foot syndrome (grades 2 3), while in this study most common side effect was grade 1 and 2 diarrhea (43.3%) followed by hand foot syndrome (35%) and rash (13.3 %). Grade 3 and 4 hand and foot syndrome was noticed in 6 patients, grade 3 and 4 diarrhea in only 4 patients

(6.6%) and grade 3 and 4 rash in 2 patients (3.3%). Lt ventricular affection was noticed in 7 cases (11.6%).

Approximately 38.1% of the reported SAEs in LEAP were possibly related to lapatinib, and the most frequently reported events were diarrhea, vomiting, and nausea.

In EGF100151, the most common AEs (> 25% incidence, any grade) reported for patients receiving lapatinib plus capecitabine were diarrhea, nausea, vomiting, hand-foot syndrome, and rash. Moreover, the most common grade 3 or 4 were diarrhea and hand-foot syndrome (21).

Cardio-toxicity was rare, although impairment of the LEVF was documented (10).

Cetin et al., reported the most frequently reported events were hand-foot syndrome, diarrhea, fatigue, anorexia, and vomiting. Moreover, the most common grade 3 or 4 AEs were diarrhea and fatigue.

In this study, tolerability data show that 45% of patients needed a lapatinib dose reduction, and 30% a treatment interruption due to toxicity, while treatment discontinuation occurred in 18.3% of the cases, this is due to the included patients was with old age and received combined treatment.

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