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Full Length Article

All-oral combination of lapatinib and capecitabine in patients with brain metastases from HER2-positive breast cancer – A phase II study

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KEYWORDS

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Abstract *Purpose:* Approximately one-third of patients with advanced, HER2 + ve breast cancer (BC) develop brain metastases (BMs). The aim of this study is to investigate efficacy and tolerability of the combination of lapatinib and capecitabine (LC) in HER2 + ve BC patients with brain metastases (BCBM).

Patients and methods: Between January 2011 and January 2013, 21 patients with HER2 + ve BCBM were included. Sixteen patients (76.19%) progressed after whole brain radiotherapy (WBRT) and 5 patients (23.81%) were treatment-naïve for BM. Patients received lapatinib (1250 mg/day continuously) and capecitabine (2000 mg/m^2 on days 1–14 of a 21-day cycle). All patients were treated with trastuzumab either in the adjuvant or metastatic setting. No patients had received prior lapatinib and/or capecitabine. End-points were response rate (RR), progression free survival (PFS), overall survival (OS) and toxicity.

Results: The overall response rate (ORR) was 33.3% (7/21) and all were partial response. For patients receiving prior WBRT and patients receiving LC as first line treatment for BCBM the ORR was 31.2% (5/16) and 40.0% (2/5) respectively. Median PFS was 5.5 months. Median OS was 11 months. Treatment-related adverse events were manageable. Grade 3–4 toxicities were hand-foot syndrome (14.3%), diarrhea (14.3%), nausea/vomiting (9.5%), mucositis (4.8%), and skin rash (4.8%).

Conclusion: The combination of LC is active and well-tolerated treatment in patients with HER2 + ve BCBM.

Introduction

Worldwide, breast cancer is the most common malignancy and cause of cancer-related death in women [1,2].

Breast cancer with brain metastases are the second most frequent secondary CNS metastases being only pre ceded by

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lung cancer [3]. Its incidence is strongly influenced by the biology of the primary tumor subtype, reaching its highest incidence in HER2-positive and TNBC subtypes and lowest in the luminal subtypes [4].

Treatment options for patients with brain metastases include surgery, stereotactic radiosurgery, whole-brain radiotherapy and steroids [5,6]. The development of effective systemic therapy for recurrent or progressed brain metastases after local treatment remains a major challenge and an urgent medical need [7].

The pattern of disease recurrence in the HER2-positive BC subtype has changed dramatically as a result of the routine use of adjuvant HER2-directed therapy. The use of adjuvant trastuzumab (Herceptin), has not only been effective in reducing the recurrence rates of HER2-positive breast cancer, but it has also altered the pattern of relapse and survival following the diagnosis of BCBM [8,9]. Interestingly, about half of patients treated with trastuzumab will either be responding to therapy or have stable disease at the time of diagnosis of BCBM; the remainder will die of progressive CNS disease [10]. While trastuzumab is relatively effective in visceral and bony disease, the brain is increasingly recognized as a sanctuary site for tumor cells due to the relative difficulty larger monoclonal antibody therapies have in penetrating the blood brain barrier (BBB) [10,11]. Evidence for this comes from the significantly lower cerebrospinal fluid levels of trastuzumab relative to plasma levels [12,13]. Interestingly, the CSF-to-serum trastuzumab concentration ratio has been shown to be improved in the setting of meningeal disease and WBRT [12].

Lapatinib which is a small molecule, has the ability to cross the BBB and acts as a reversible inhibitor of the intracellular tyrosine kinase domain of two members of the HER family, HER1 (EGFR-1) and HER2 (EGFR-2) through binding to the cytoplasmic ATP-binding site of the kinase and blocks receptor phosphorylation and activation, thereby preventing subsequent downstream signaling events [1,10,14].

Lapatinib markedly decreased thymidylate synthase (TS) expression, thus allowing capecitabine for better inhibition of the remaining enzyme activity. Additionally, it was suggested that concomitant administration is more likely to ensure better efficacy, as compared with sequential use [15].

On the basis of this evidence, we initiated this study to investigate tolerability and efficacy of the combination of LC in HER-2 positive BCBM.

Patients and methods

Patient eligibility criteria

Between January 2011 and January 2013, 21 patients with brain metastases HER2-positive BC in the Clinical Oncology Department, Faculty of Medicine, Tanta University Hospital were included. Sixteen patients (76.19%) progressed after WBRT and 5 patients (23.81%) were treatment-naïve for brain metastases. Brain metastases were confirmed by computed tomography scan or magnetic resonance imaging with at least one measurable brain lesion of a size of 10 mm or greater in diameter. All patients received prior treatment with trastuzumab either in the adjuvant setting or for the metastatic disease.

Patients fulfilled the following criteria: age between 18 and 70 years with HER2 + ve (defined as 3 + immunohistochemistry or evidence of gene amplification by fluorescence in situ hybridization) BC, Eastern Cooperative Oncology Group (ECOG) performance status (PS) of $\leqslant 2$, adequate bone marrow reserve (WBC count $\geqslant 3.5 \times 10^9$/L, absolute neutrophil count of $\geqslant 1.5 \times 10^9$/L, platelets $\geqslant 100 \times 10^9$/L, and hemoglobin $\geqslant 10$ gm/dL), adequate renal function (measured creatinine clearance $\geqslant 60$ mL/min) and adequate liver function (transaminases less than $2 \times$ upper normal limit, and serum bilirubin concentrations below 1.5 mg/dL).

Patients suffering from secondary malignancy or concurrent serious, uncontrolled medical illness (e.g. persistent immune-compromised states, uncontrolled infection, severe peripheral neuropathy, and clinically significant cardiac disease) were excluded from this study. Also patients with prior exposure to lapatinib or capecitabine, malabsorption or other gastrointestinal disease affecting absorption of oral medications, pregnancy or lactation and male sex were excluded.

All radiotherapy, chemotherapy, hormonal therapy, and/or trastuzumab had to be discontinued at least 2 weeks before initiation of protocol treatment. Concomitant bisphosphonates, mannitol, and corticosteroids were allowed, provided that the corticosteroid dose was stable for at least 1 week before inclusion.

Design of the study

This study is a prospective single-arm phase II single institution study. The Ethics Committee in the Faculty of Medicine, Tanta University, granted protocol approval and all patients signed an informed consent before the initiation of any treatment.

Treatment plan and dose medication

Patients received lapatinib 1250 mg once daily every morning continuously and capecitabine 2000 mg/m^2/day, divided into two doses, on days 1–14, every 21 days.

Cycles were administered on an outpatient basis. Adequate hematological and within normal range organ functions were insured prior to each cycle. Chemotherapy was discontinued in case of disease progression or major toxicities.

Adverse events were monitored throughout the study. A complete resolution of hematologic and non-hematologic toxicity was required except for alopecia and fatigue. If toxicities did not resolve, then a 1-week delay was allowed.

Patient assessment

Assessment of clinical benefit

A tumor response assessment was performed after every three cycles of treatment. Pre- and on-treatment monitoring consisted of medical history, physical and neurological examination, CT-scan of the chest, abdomen and pelvis, and MRI or CT scan of the brain. Criteria of complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD) were based on the standard definitions according to RECIST 1.0 criteria [16], with the overall response rate, including complete response and partial response. Progression of non-measurable CNS lesions, tumor-related increase in steroid dose, new or worsening tumor-related symptoms were considered as disease progression.

Assessment of toxicity

Patients were assessed for adverse events at each site with clinical and laboratory evaluations every 3 weeks and cardiac monitoring, by ECHO, every 12 weeks. Toxicity grading was based on the common terminology criteria for adverse events (NCI-CTC, version 3.0) [17].

Primary and secondary endpoints

The primary endpoints of the study were overall response and toxicity. Secondary end points were the progression-free survival and overall survival.

Statistical analysis

Overall-survival (OS) rates were calculated from the start of the oral combination of LC in HER-2 positive BCBM to the time of the last follow-up visit or death using the Kaplan–Meier method [18] with SPSS [Statistical package] (version 12.0). Progression-free survival was the time elapsed from the date of initiation of oral combination of LC to the date of first evidence of disease progression or death in the absence of disease progression. Log rank is used for comparison of curves. Mean and standard deviation were estimates of quantitative data. The 95% confidence intervals (95% CIs) were calculated with the exact method. Fisher exact test was used for qualitative data. All P values were two-tailed; a value of $\leqslant 0.05$ was considered significant.

Results

Patient characteristics

Twenty-one patients were recruited in the study with pathologically proven HER2+ BC who had developed BMs confirmed by magnetic resonance imaging or computed tomography scan. All our patients received at least 2 doses of LC as systemic therapy after the development of BMs.

The base line characteristics are listed in Table 1, with the mean age 45.4 ± 8.0 years (range; 36–69 years). The majority of cases were T2 or greater, node positive, grade II, and of ECOG performance status of $\leqslant 1$. Fourteen patients (66.7%) were premenopausal and 7 patients (33.3%) were postmenopausal. Twelve patients (57.1%) had positive progesterone receptors (PR), while 14 (66.7%) patients had positive estrogen receptors (ER), and 9 patients (42.9%) had positive ER and PR. In 6 patients (28.6%) HER2+ gene amplification was confirmed by fluorescence in situ hybridization test. All patients had received prior trastuzumab-based systemic therapies for either adjuvant setting or metastatic disease. Local treatment had been delivered for BMs in 16 patients (76.2%) in the form of whole cranial radiotherapy (WBRT). Five patients (23.8%) had not received any prior local treatment for BMs with lapatinib and capecitabine (LC) as the first systemic option after the development of BMs in these 5 patients (23.8%).

Table 1 Patients' and tumor characteristics of the 21 patients with BMs from HER2+ breast cancer treated with LC.

Characteristic	No. patients (%)
Age (years)	
Mean	45.4
Range	(36–69)
ECOG performance status	
0	5 (23.8%)
1	10(47.6%)
2	6 (28.6%)
Menopausal status	
Pre	14 (66.7%)
Post	7 (33.3%)
Initial tumor grade	
Grade I	1 (4.7%)
Grade II	14 (66.7%)
Grade III	6 (28.6%)
Lymph nodes dissected	
(median, range)	20 (8–25)
Involved lymph node	
(median, range)	7 (0–24)
ER	
+ve	14 (66.7%)
-ve	7 (33.3%)
PR	
+ve	12 (57.1%)
-ve	9 (42.9%)
ER/PR+ve	
Yes	9 (42.9%)
No	12 (57.1%)
Her-2-neu positivity	
IHC: 3 + positive	15 (71.4%)
FISH amplified	6 (28.6%)
Previous systemic therapy	
Trastuzumab + endocrine therapy	1 (4.7%)
Trastuzumab + FEC or AC	6 (28.6%)
Trastuzumab + AT	14 (66.7%)
Extracranial metastases	
Yes	19 (90.5%)
No	2 (9.5%)
Visceral metastases	16 (76.2%)
Number of BMs	
<3	9 (42.9%)
$\geqslant 3$	12 (57.1%)
Local treatment for BMs, n (%)	
None	5 (23.8)
Whole cranial radiotherapy	16 (76.2)

ER, estrogen receptors; PR, progesterone receptors; FEC, 5-flouorauracil + epirubicin + cyclophosphamide; AT, adriamycin + taxanes.

Treatment administration

A total of 84 chemotherapy cycles were administered. Patients were treated with a median number of 4 cycles of lapatinib and capecitabine (range 2–21 cycles).

The median treatment duration of lapatinib plus capecitabine was 12.1 weeks. The maximum treatment duration was 63 weeks.

Activity of both drugs (patient response to those drugs)

The overall response rate was 33.3 (7/21) for all patients and no one had complete response. Stable disease (SD) was recorded in

6 patients (28.6%), while progressive disease (PD) was recorded in 8 patients (38.1%) (Table 2).

For patients receiving prior cranial radiotherapy (WBRT) and patients receiving LC as first line treatment for BMs the overall response rate was 31.2% (5/16) and 40.0% (2/5) respectively.

Toxicity

The LC combination therapy was generally well-tolerated. Most of the adverse events were of grade 1–2 (Table 3). The most common grade 3–4 toxicities included hand-foot syndrome (14.3%), diarrhea (14.3%), nausea/vomiting (9.5%), mucositis (4.8%) and rash (4.8%). Grade 3 neutropenia was observed in one patient. None of the patients developed symptomatic congestive heart failure or an asymptomatic decline in LVEF to less than 15% of the lower limit of the normal range. No patient was taken off the treatment because of toxicity and there was no treatment-related death.

Dose reduction was performed in 6 patients (28.57%) with 25% reduction for both drugs. Chemotherapy was interrupted for 1 week in 2 patients (9.5%). Five patients received less than 3 cycles due to rapid disease progression.

Survival

Twenty-one patients were recruited in the study between January 2011 and January 2013. Patients were followed up until June 2014. At the time of analysis, the median follow up duration was 11.0 months (Range; 1.57–35.57 months). All our patients were followed up regularly as mentioned previously in patients and methods, with no one having lost follow up in this study.

Median progression free survival (PFS) was 5.five months (Range; 1.1–22.0 months), (Fig. 1, Table 4).

Median PFS was 4.1 months, for the 16 (76.2%) patients for whom prior local treatment had been delivered for BMs in the form of whole cranial radiotherapy, compared to 18.3 months, (P = < 0.001), for the 5 (23.8%) patients who received LC as the first therapeutic option after the development of BMs, (Fig. 2, Table 4).

Table 2 Treatment response on the 21 patients with BMs from HER2 + breast cancer treated with LC.

Evaluable patients	No.	%
Partial response	7	33.3
Stable disease	6	28.6
Progressive disease	8	38.1

Table 3 Treatment related adverse events on patients with BMs from HER2 + breast cancer treated with LC.

	Any grade N (%)	Grade 3–4 N (%)
Hand-foot syndrome	14 (66.6)	3 (14.3)
Diarrhea	13 (61.9)	3 (14.3)
Nausea/vomiting	11 (52.4)	2 (9.5)
Neutropenia	10 (47.6)	1 (4.8)
Mucositis	8 (38.1)	1 (4.8)
Rash	7 (33.3)	1 (4.8)
Bilirubin increase	5 (23.9)	0.0

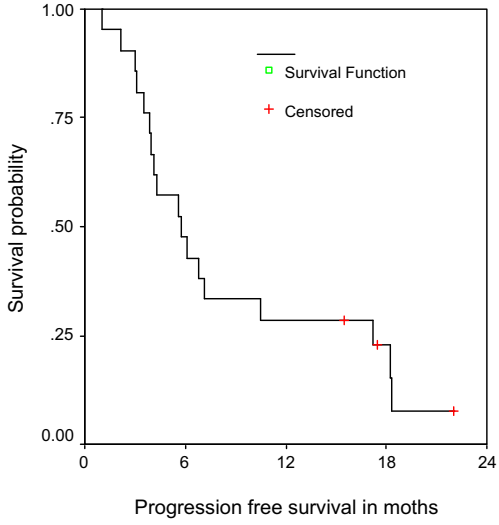

Figure 1 Kaplan–Meier curve of progression-free survival. Median PFS time was 5.5 months.

Median PFS was 10.5 months, and 3.5 months, for patients with the number of BMs < 3 and patients with the number of BMs ⩾ 3 respectively (P = < 0.001), (Fig. 3, Table 4).

The median PFS was 6.1 months, compared to 4.1 months, for the 15 patients with ECOG performance status of ⩽ 1 and the 6 patients with ECOG performance status of 2 respectively, (P = 0.141), (Table 4).

The 6 month and 12 month overall survival (OS) for all patients were 80.6% and 45.6%, respectively, (Fig. 4, Table 5).

The median OS was 9.1 months, for the 16 patients (76.2%) for whom prior local treatment had been delivered for BMs in the form of whole cranial radiotherapy. However, the median OS was not reached, for the 5 patients (23.8%) who had received LC as the first therapeutic option after the development of BMs (P = < 0.001), (Table 5).

Median OS was 23.8 months, and 7.1 months, for patients with the number of BMs < 3 and patients with the number of BMs ⩾3 respectively, (P = < 0.001), (Fig. 5, Table 5).

The median OS was 11.3 months, and 6.2 months, for the 15 patients with ECOG performance status of ⩽ 1 and the 6 patients with ECOG performance status of 2 respectively, (P = 0.271), (Table 5).

Discussion

The CNS is an important site for metastatic dissemination causing substantial morbidity and mortality in patients with HER2+ BC [4,10,11,19]. Currently, there are limited therapeutic options for patients with HER2+ breast cancer who develop progressive CNS disease after cranial radiotherapy [7]. So, agents more efficient at penetrating the CNS to prevent or treat CNS metastases are urgently needed. The use of lapatinib with capecitabine (Xeloda) (LC) in treatment of CNS metastases in patients with HER2+ MBC, has been proved to improve the response rate and prognosis of patients with HER2+ BCBM [1,20].

Table 4 Progression free survival of patients with BMs from HER2 + breast cancer treated with LC according to different prognostic and predictive factors.

Parameter	No. of patients (%)	Progression free survival			*p*-Value
		Median(ms)	6 ms(%)	12 ms(%)	
All patients	21 (100)	5.5	42.86	28.57	
ECOG performance status					
⩽1	15 (71.4)	6.1	51.2	31.7	0.141
2	6 (28.6)	4.1	30.7	20.1	
Prior local ttt. for BMs					
None	5 (23.8)	18.3	100.0	100.0	<0.001
Whole cranial Rth	16 (76.2)	4.1	31.3	6.3	
Hormonal receptors					
+ve	14 (66.7)	8.1	61.1	32.9	0.098
-ve	7 (33.3)	5.5	42.9	25.2	
Number of BMs					
<3	9 (42.9)	10.5	83.3	50.0	<0.001
⩾3	12 (57.1)	3.5	0.0	0.0	

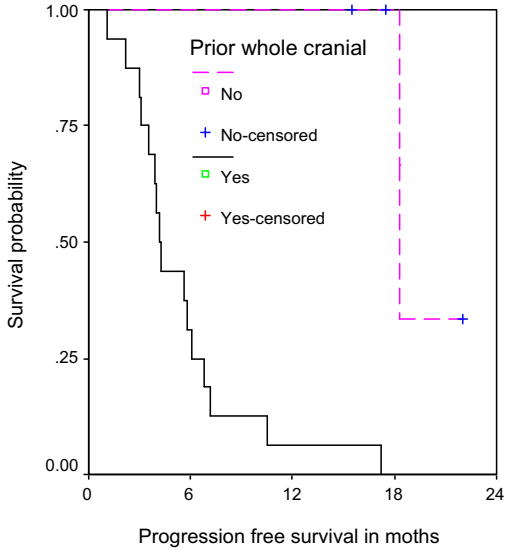

Figure 2 Kaplan–Meier curve of PFS for the 16 patients for whom prior whole cranial radiotherapy had been delivered and the 5 patients who received LC as the first therapeutic option after the development of BMs.

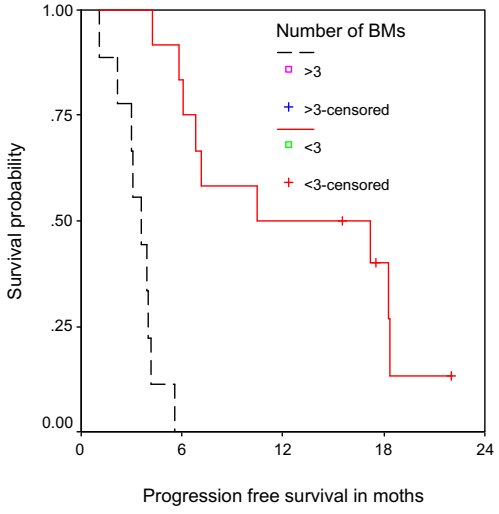

Figure 3 Kaplan–Meier curve of PFS for patients with the number of BMs < 3 and patients with the number of BMs ⩾ 3.

We used oral lapatinib (1250 mg/day continuously) and capecitabine (2000 mg/m^2 on days 1–14 of a 21-day cycle) continuously unless there was discontinuation due to severe toxicity or disease progression. This treatment schedules and doses were selected based on previous studies [19,20].

Our treatment schedule appeared to have good clinical efficacy (33.3% overall response rate). Lin et al. [21] in the lapatinib plus capecitabine group of his randomized study, reported a response rate of 38.5% which was comparable with that reported in a retrospective study of outcome after such combination treatment (31.8%) [19]. These data are also consistent with those from analysis of patients with CNS metastasis included in lapatinib expanded access programmes in the UK and France [22,23]. This is also consistent with previous published study by Cetin et al. [1] who reported a response rate of 27.1%. These results suggest that the combination of lapatinib plus capecitabine has activity for the treatment of brain metastases in patients with HER2-positive breast cancer.

Metro et al. [19] reported that the best response rate (75%) was remarkably, observed with LC in four patients who had not received any prior local treatment for BMs. This finding might suggest that systemic treatment with LC is active on BMs in patients who have not been previously treated with cranial radiotherapy. Similarly, Bachelot et al. [20] observed that the response rate of 65.9%, (95% CI 50.1–79.5) has been developed in a trial in which patients received this combination as their first metastatic brain directed therapy and prior to WBRT. The greater proportion of responses seen in this study than in other studies [7,21–24] is most likely related to the fact that this study was restricted to WBRT naive patients. The current study reported an ORR of 31.2% (5/16), for patients receiving prior cranial radiotherapy (WBRT) compared to 40.0% (2/5) for patients receiving LC as the first line of treatment for BCBM prior to WBRT, supporting the option of delaying WBRT with its associated toxicities, and instead initiating a trial of systemic therapy at the time of diagnosis of

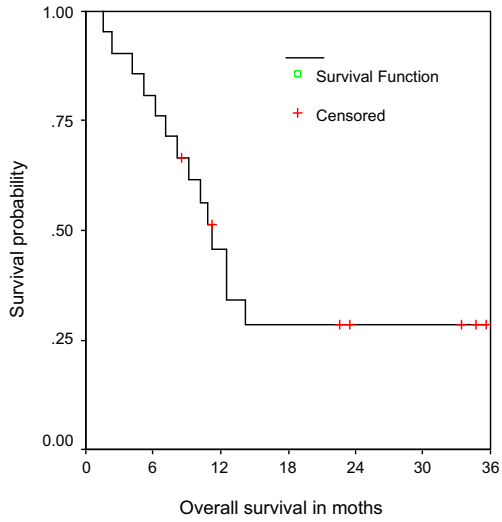

Figure 4 Kaplan–Meier curve of overall survival. Median OS time was 11 months.

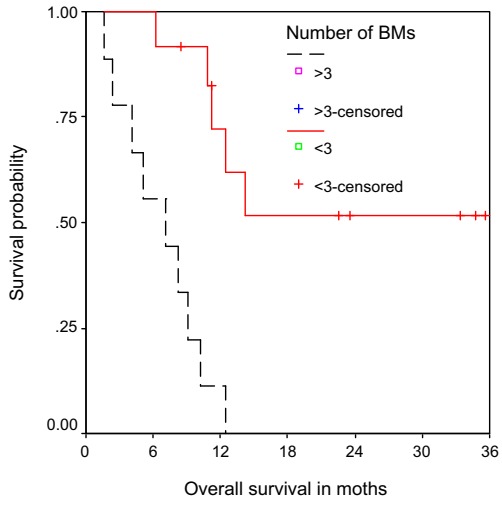

Figure 5 Kaplan–Meier curve of OS for patients with number of BMs <3 and $\geqslant 3$.

brain metastases. This also can allow concomitant treatment of extra-CNS metastatic sites which can contribute a survival advantage if cranial disease is controlled [25].

In our study, the median PFS was 5.5 months. Bachelot et al. [20] reported that the median PFS in published series on the combination of lapatinib plus capecitabine for the treatment of brain metastases from HER2-positive breast cancer regimen was 5.5 months [20]. Metro et al. [19] reported that the combination of chemotherapeutic agents lapatinib plus capecitabine has been used in the treatment of brain metastases from HER2-positive breast cancer with a comparable median PFS of 5.6 months (95% confidence interval 4.4–6.8) in this patient group. Other trials reported a median PFS of 3.7–5.6 months [7,21–24].

Treatment with lapatinib after the development of BMs was one of the factors associated with prolonged survival from the diagnosis of BMs [26]. In our study, the median overall survival (OS) of 11 months was comparable with that reported in other trials which published on the OS with lapatinib plus capecitabine combination which ranged from 6.3 to 13 months in patients who had received prior trastuzumab combination therapies [7,21–24].

In our study, this combination therapy was generally well-tolerated. Most of the adverse events were of grade 1–2. The most common grade 3–4 toxicities included hand-foot syndrome (14.3%), diarrhea (14.3%), nausea/vomiting (9.5%), mucositis (4.8%) and rash (4.8%). Grade 3 neutropenia was observed in one patient. None of the patients developed symptomatic congestive heart failure or an asymptomatic decline in LVEF to less than 15% of the lower limit of the normal range. There was no treatment-related death. Dose reduction was performed in 6 patients (28.57%) with 25% reduction for both drugs. Chemotherapy was interrupted for 1 week in 2 patients (9.5%).The frequency of these toxicities was somewhat lower than that reported by Bachelot et al. [20] and Sutherland et al. [22] but higher than that reported in Lin et al. study [7]. Bachelot et al. [20] reported that about half of patients had grade 3 or grade 4 toxicities, mainly diarrhea and hand-foot syndrome, leading to treatment discontinuation in four patients, without recorded cases of toxic death. Sutherland

Table 5 Overall survival of patients with BMs from HER2 + breast cancer treated with LC according to different prognostic and predictive factors.

Parameter	No. patients (%)	Overall survival			*p*-Value
		Median (ms)	6 ms (%)	12 ms (%)	
All patients	21 (100)	11.0	80.6	45.6	
ECOG performance status					
$\leqslant 1$	15 (71.4)	11.3	85.7	40.8	0.271
2	6 (28.6)	6.2	57.1	21.4	
Hormonal receptors					
+ve	14 (66.7)	11.3	85.7	42.9	0.827
-ve	7 (33.3)	10.8	78.6	40.2	
Prior local ttt. for BMs					
None	5 (23.8)	-	100.0	100.0	<0.001
Whole cranial Rth	16 (76.2)	9.1	75.0	26.4	
Number of BMs					
<3	9 (42.9)	23.8	91.7	72.2	<0.001
$\geqslant 3$	12 (57.1)	7.1	55.6	0.0	

et al. [22] reported that serious adverse events (SAEs) in the overall UK population were again higher with that of our study. In the UK patients, a total of 25% serious adverse events were reported. The most frequently reported serious adverse events were diarrhea, vomiting, nausea, dehydration and palmar-plantar erythrodysaesthesia syndrome. Also in the UK study population, two subjects experienced a decreased ejection fraction and ten serious haepatobiliary events were reported [22]. In Lin et al. study [7] palmar-plantar erythrodysesthesia (8%), nausea (8%), vomiting (6%), and diarrhea (4%) constituted the most common grade 3 adverse events. However, one fatal serious adverse event was reported in a patient who died of a small intestinal perforation, but it was deemed by the treating physician as unrelated to lapatinib plus capecitabine [7].

Conclusion

From our study, we concluded that the combination of lapatinib plus capecitabine (LC) is an active combination against BMs from HER2+ BC in patients naive for both lapatinib and capecitabine. Also, our findings suggest that the combination of LC may further improve the prognosis in previously untreated BMs in patients with HER2+ BC. However, head to head randomized phase 3 studies are advocated to confirm the clinical benefits for patients in terms of survival, cognitive function, and quality of life.

Conflict of interest

We have no conflict of interest to declare.

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