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Lapatinib plus Capecitabine for Brain Metastases in Patients with Human Epidermal Growth Factor Receptor 2-Positive Advanced Breast Cancer: A Review of the Anatolian Society of Medical Oncology (ASMO) Experience

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Keywords
HER2 · Metastatic breast cancer · Lapatinib · Brain metastases

Summary
Background: We investigated the clinical outcome of patients with brain metastases (BMs) from human epidermal growth factor receptor 2-positive (HER2+) metastatic breast cancer (MBC) treated with lapatinib and capecitabine (LC). **Patients and Methods:** A total of 203 patients with HER2+ MBC, who had progressed after trastuzumab-containing chemotherapy, were retrospectively evaluated in 11 centers between September 2009 and May 2011. 85 patients who had developed BMs before the initiation of treatment with LC were included. All patients had received prior cranial radiotherapy. All patients were treated with the combination of lapatinib (1,250 mg/day continuously) and capecitabine (2,000 mg/m^2 on days 1–14 of a 21-day cycle). **Results:** The median follow-up was 10.5 months (range 1–38 months). An overall response rate of 27.1% was achieved, including complete response in 2 (2.4%) and partial response in 21 (24.7%) patients. Median progression-free survival was 7 months (95% confidence interval (CI) 5–9), with a median overall survival of 13 months (95% CI 9–17). The most common side effects were hand-foot syndrome (58.8%), nausea (55.3%), fatigue (48.9%), anorexia (45.9%), rash (36.5%), and diarrhea (35.4%). Grade 3–4 toxicities were hand-foot syndrome (9.4%), diarrhea (8.3%), fatigue (5.9%), and rash (4.7%). There were no symptomatic cardiac events. **Conclusion:** LC combination therapy was effective and well-tolerated in patients with HER2+ MBC with BMs, who had progressive disease after trastuzumab-containing therapy.

Schlüsselwörter
HER2 · Metastasiertes Mammakarzinom · Lapatinib · Hirnmetastasen

Zusammenfassung
Hintergrund: Wir haben das klinische Outcome von Patientinnen mit Hirnmetastasen eines HER2 (human epidermal growth factor receptor 2)-positiven metastasierten Mammakarzinoms unter Behandlung mit Lapatinib und Capecitabin (LC) evaluiert. **Patientinnen und Methoden:** Insgesamt wurden 203 Patientinnen mit HER2-positivem metastasierten Mammakarzinom, bei denen es zu einem Krankheitsfortschreiten unter Trastuzumab enthaltender Therapie gekommen war, zwischen September 2009 und Mai 2011 in 11 Behandlungszentren retrospektiv evaluiert. 85 Patientinnen, die vor dem Beginn der LC-Behandlung Hirnmetastasen entwickelt hatten, wurden in die Studie aufgenommen. Alle Patientinnen waren zuvor einer kranialen Radiotherapie unterzogen worden, und alle erhielten gleichermaßen eine Kombination aus Lapatinib (1250 mg/d kontinuierlich) und Capecitabine (2000 mg/m^2 an Tag 1–14 eines 21-tägigen Zyklus). **Ergebnisse:** Das mittlere Follow-Up betrug 10,5 Monate (Spanne 1–38 Monate). Eine Gesamtansprechrate von 27,1% wurde erreicht, inklusive eines kompletten Ansprechens bei 2 (2,4%) und eines Teilansprechens bei 21 (24,7%) Patientinnen. Das mittlere progressionsfreie Überleben war 7 Monate (95%-Konfidenzinterval (KI) 5–9) mit einem mittleren Gesamtüberleben von 13 Monaten (95%-KI 9–17). Die häufigsten Nebenwirkungen waren Hand-Fuß-Syndrom (58,8%), Übelkeit (55,3%), Fatigue (48,9%), Anorexie (45,9%), Hautausschlag (36,5%) und Durchfall (35,4%). Als Toxizitäten vom Grad 3–4 traten Hand-Fuß-Syndrom (9.4%), Durchfall (8,3%), Fatigue (5,9%) und Hautausschlag (4,7%) auf. Symptomatische kardiovaskuläre Nebenwirkungen wurden nicht beobachtet. **Schlussfolgerung:** Die LC-Kombinationstherapie war bei Patientinnen mit HER2-positivem metastasierten Mammakarzinom mit Hirnmetastasen, bei denen es nach trastuzumabhaltiger Therapie zu einem Progress gekommen war, effektiv und wurde gut toleriert.

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Introduction

Approximately 20–25% of all breast cancers are human epidermal growth factor receptor 2-positive (HER2+) and have historically been associated with poorer disease-free survival (DFS) and overall survival (OS) [1]. For patients with HER2+ metastatic breast cancer (MBC), the use of humanized monoclonal antibody trastuzumab (Herceptin®, Genentech, San Francisco, CA, USA) in combination with chemotherapy has become the standard of care. Approximately one third of patients with MBC treated with trastuzumab-containing therapy develop brain metastases (BMs) [2, 3]. Concerns have also been raised about high rates of BMs following systemic response to trastuzumab. Trastuzumab does not fully cross the blood-brain barrier, making the brain a 'sanctuary' site [4, 5]. Recently, a literature-based meta-analysis of randomized phase III clinical trials including trastuzumab as adjuvant therapy for early-stage breast cancer demonstrated that patients receiving trastuzumab therapy had a significantly higher risk for developing central nervous system (CNS) metastases compared to the patients treated with non-trastuzumab-containing regimens (relative risk 1.57, 95% confidence interval (CI) 1.03–2.37) [6]. Increased incidence of BMs in MBC limits the benefits of new systemic treatment modalities. Current treatments for BMs are palliative, including stereotactic radiosurgery or whole-brain radiotherapy (WBRT). Treatment options for CNS metastases from HER2+ MBC remain limited, while only a few prospective trials have been conducted [7, 8]. Lapatinib (Tykerb®, GlaxoSmithKline, Philadelphia, PA, USA) was approved in combination with capecitabine in patients with HER2+ MBC after progression under trastuzumab treatment based on a pivotal phase III study [9]. Compared to trastuzumab, lapatinib shows restricted but improved brain uptake by reaching levels up to one-quarter of those in plasma [10]. Lapatinib may reduce the risk of disease progression in the CNS based on the results from exploratory analyses performed from the pivotal phase III trial [11]. In this regard, the present study was undertaken to evaluate the clinical efficacy and adverse effect profile of lapatinib + capecitabine (LC) combination therapy in patients with HER2+ MBC and BMs, who progressed after trastuzumab therapy.

Patients and Methods

Patients

A total of 203 patients with HER2+ MBC, who received LC after progression following trastuzumab-containing chemotherapy, were retrospectively identified from 11 centers between September 2009 and May 2011. Of those, 85 patients who had developed BMs before the initiation of LC treatment were eligible to be included in this retrospective multicenter study. BMs were confirmed by magnetic resonance imaging or computed tomography scan. Eligible patients were females, ≥ 18 years of age, with HER2+ MBC and 3+ staining by immunohistochemistry or evidence of gene amplification by fluorescence in situ hybridization. Patients had metastatic disease that progressed on their most recent treatment regimen which must have included trastuzumab. Patients were required to have a left ventricular ejection fraction (LVEF) within institutional normal limits, an absolute neutrophil count of at least 1,000/µl, a platelet count of at least 75,000/µl, bilirubin no more than 1.5 times the upper limit of normal (ULN), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) no more than 5 times the ULN, and a creatinine clearance of at least 25 ml/min.

Treatment

Patients were treated with lapatinib 1,250 mg orally once daily plus capecitabine 1,000 mg/m^2 orally twice daily on days 1–14 every 21 days until disease progression. Dose reductions and delays for lapatinib- and/or capecitabine-related toxic effects were done by the treating physician. Data on demographics, clinical outcome, and toxicity were collected based on retrospective evaluation of medical records for the descriptive analyses.

Evaluation of Efficacy

Overall response rate (ORR; complete response (CR) plus partial response (PR)) was determined in the CNS and non-CNS cases. CNS responses were classified according to modified Response Evaluation Criteria in Solid Tumors (RECIST) [12]. Non-CNS response was also assessed by RECIST. Date of progression was recorded as the first documented progression at any site in either CNS or non-CNS. Patients continued study treatment until they experienced unacceptable toxicity, or until progressive disease (PD) occurred. Progression-free survival (PFS) was the time elapsed from the date of initiation of LC to the date of the first evidence of PD or death in the absence of PD. OS was defined as the period from the first day of treatment until the date of last follow-up or death.

Evaluation of Safety

Patients were monitored for serious adverse events (SAEs) according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE, version 3.0) which grades events as mild (grade 1), moderate (grade 2), severe (grade 3), life-threatening or disabling (grade 4), or fatal (grade 5). Concerning cardiac safety, a cardiac event was defined as a decline in the LVEF that was symptomatic, regardless of the degree of decline or was asymptomatic but with a relative decrease of 20% or more from baseline to a level below the institution's lower limit of the normal range. Lapatinib was discontinued in patients with symptomatic cardiac events.

Statistical Analysis

Statistical analysis was carried out using computer software (SPSS version 17.0, SPSS Inc. Chicago, IL, USA). Kaplan-Meier curves were used to estimate DFS and OS, and groups were compared by the log-rank test. All prognostic variables determined to be significant in univariate analysis were included in multivariate analysis using the Cox proportional hazards model. Data were expressed as mean (standard deviation (SD)), minimum-maximum, percent (%), and 95% CI where appropriate. A p value of < 0.05 was considered statistically significant.

Results

Patients

Patient demographics and baseline clinical characteristics are summarized in table 1. The median age was 47 years (range 25–72 years). All patients had multiple BMs. All patients had received prior trastuzumab-based therapies for adjuvant or

Table 1. Demographic characteristics of patients with brain metastases from HER2+ breast cancer treated with lapatinib and capecitabine

Age, median (range), years	47 (25–72)
ECOG performance status, n (%)	
0	18 (21.2)
1	52 (61.2)
2	14 (17.6)
Hormone receptor status, n (%)	
ER- and/or PR-positive	47 (55.3)
ER- and PR-negative	38 (44.7)
HER2 positivity, n (%)	
IHC 3+	68 (80)
FISH amplified	17 (20)
Extracranial metastases, n (%)	
No	3 (3.5)
Yes	82 (96.5)
Metastatic sites, n (%)	
Liver	45 (52.9)
Bone	54 (63.5)
Lung	35 (41.1)
Other (local, axilla, skin)	10 (1.1)
Number of metastatic sites, n (%)	
< 3	38 (44.7)
≥ 3	47 (55.3)
Number of prior chemotherapy, n (%)	
(Neo)-adjuvant	68 (80)
Metastatic 1	2 (2.4)
Metastatic 2	26 (30.6)
Metastatic 3	37 (43.5)
Metastatic > 3	20 (23.6)
Previous therapy, n (%)	
Anthracyclines	71 (83.5)
Taxanes	81 (95.2)
Capecitabine	13 (15.3)
Vinorelbine	17 (20)
Gemcitabine	7 (8.2)
Trastuzumab-based therapy, n (%)	
Trastuzumab + chemotherapy	79 (93)
Trastuzumab + endocrine therapy	6 (7)
Duration of prior trastuzumab, median (range), weeks	43 (7–134)
Prior CNS radiation, n (%)	
WBRT only	85 (100)
SRS only	0 (0)

ER = Estrogen receptor; PR = progesterone receptor; IHC = immunohistochemistry; FISH = fluorescence in situ hybridization; CNS = central nervous system; WBRT = whole brain radiotherapy; SRS = stereotactic radiosurgery.

Table 2. Efficacy parameters in patients with brain metastases from HER2+ breast cancer treated with lapatinib and capecitabine (n = 85)

End point	
Overall survival, median (range), months	13 (9–16.9)
Progression-free survival median (range), months	7 (5.6–8.3)
Overall response rate (ORR), n (%)	23 (27.1)
Complete response (CR), n (%)	2 (2.4)
Partial response (PR), n (%)	21 (24.7)
Stable disease (SD), n (%)	35 (41.2)
Progressive disease (PD), n (%)	27 (31.8)
Clinical benefit rate (ORR + SD), n (%)	58 (68.3)

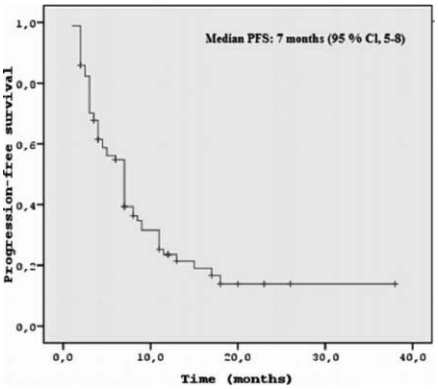

Fig 1. Progression-free survival. Median PFS was 7 months (95% CI 5–9).

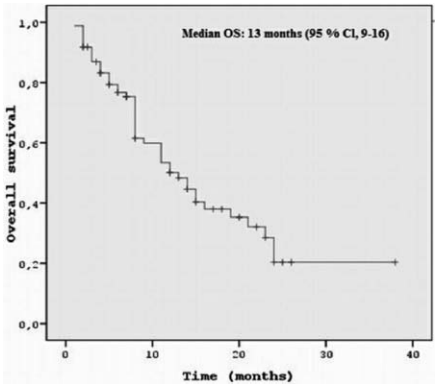

Fig 2. Overall survival. Median OS was 13 months (95%CI 9–16).

metastatic disease, as well as WBRT. LC was administered as the first-line systemic therapy following WBRT after the development of BMs. Previous treatment with capecitabine-based therapies for metastatic disease was evident in 13 patients. The median duration of previous treatment with trastuzumab was 43 weeks (range 7–134). Of 85 tumors, 47 (55.3%) were estrogen receptor (ER)- or progesterone receptor (PR)-positive, and 38 (44.7%) tumors were negative for both receptors.

Efficacy

Among all 85 patients, 2 (2.4%) achieved a CR, 21 (24.7%) a PR, and 35 (41.2%) SD; 27 (31.8%) patients had PD, resulting in an ORR of 27.1%. 58 (68.3%) patients had clinical benefit (ORR + SD) (table 2). The described response rates were obtained in the CNS and non-CNS sites. The median follow-up time from the initiation of LC was 10 months (range 1–38 months). The median duration of treatment with LC was 7 months (range 2–38 months). All 85 patients were included in the analysis of PFS and OS from the start of LC. The median PFS was 7 months (95% CI 5–10) (fig. 1). At the time of this analysis, 23 of the 85 patients had not yet experienced either intra- or extracranial disease progression and were still receiving LC. 47 patients died, and the median OS from the start of LC was 13 months (95% CI 9–16) (fig. 2).

Survival Outcomes after the Diagnosis of Brain Metastasis

All 8 potential predictive covariates with corresponding univariate analyses are presented in table 3. Clinical features that were significantly associated with poor OS included poor performance status, PFS ≤ 6 months, number of metastatic site ≥ 3, and failure to respond to treatment according to

Table 3. Risk factors determining survival after the onset of brain metastasis in HER2-positive metastatic breast cancer

Parameter	Patients, n		Median OS, months	Log rank p value	Multivariate analysis		
	died	total			OR	95% CI	p value
Age				0.572			
≤ 50 years	31	54	14				
> 50 years	16	31	11				
Number of metastatic site				0.036			
3 <	16	38	16		1.000		
3 ≥	31	47	12		1.056	0.544–2.052	0.872
PFS				0.0001			
> 6 months	14	39	23		1.000		
≤ 6 months	33	46	8		4.406	2.315–8.387	0.0001
Median duration of prior trastuzumab				0.627			
> 36 weeks	26	43	15				
≤ 36 weeks	21	42	11				
Therapeutic response				0.0001			
Responders	22	56	16		1.000		
Non-responders	25	29	8		1.273	0.623–2.602	0.508
ECOG PS				0.003			
0–1	34	70	15		1.000		
2	13	14	5		2.212	1.156–4.233	0.017
Hormone receptor status				0.797			
ER- and/or PR-positive	25	47	14				
ER- and PR-negative	22	38	11				
Liver metastases				0.103			
No	17	39	19				
Yes	30	46	12				

OS = overall survival; OR = odds ratio; CI = confidence interval; PFS = progression-free survival; PS = performance status; ER = estrogen receptor; PR = progesterone receptor.

Table 4. Adverse events in patients with brain metastases from HER2+ breast cancer treated with lapatinib and capecitabine

Adverse event	Any grade, n (%)	Grade 3–4, n (%)
Hand-foot syndrome	50 (58.8)	8 (9.4)
Diarrhea	30 (35.4)	7 (8.3)
Fatigue	50 (58.9)	5 (5.9)
Nausea	47 (55.3)	6 (7.1)
Rash	31 (36.5)	4 (4.7)
Anorexia	39 (45.9)	3 (3.6)

RECIST criteria. In the resulting Cox proportional hazards model (table 3), duration of PFS (> 6months vs. ≤ 6months) was determined to be the single adverse prognostic factor that was the independent predictor of short survival (p = 0.001). There was no significant survival advantage after lapatinib treatment in hormone receptor-positive patients compared with hormone receptor-negative patients in terms of PFS (median 7 months in both groups) and OS (median 14 vs. 11 months)

Adverse Events

All patients were assessable for toxicity. Grade 3 and 4 treatment-related toxicities are listed in table 4. The most common adverse events were hand-foot syndrome and fatigue which improved with supportive measures and/or dose reductions in most cases. No patient was taken off the treatment because of toxicity. 2 patients experienced grade 4 diarrhea, and 1 patient each experienced grade 4 anorexia, stomatitis, rash, and fatigue. Concerning cardiac surveillance and cardiotoxicity, none of the patients developed symptomatic congestive heart failure or an asymptomatic decline in LVEF to less than 50%.

Discussion

The CNS is an important sanctuary site for metastatic dissemination causing substantial morbidity and mortality in patients with HER2+ MBC. Our retrospective evaluation of safety and efficacy of LC in this population with BMs showed a 27.1% ORR similar to previous experience in the literature [12–17]. Moreover, survival outcomes including PFS of 7 months and OS of 13 months were similar to the literature confirming the efficacy of LC in BMs of HER2+ MBC patients.

BMs are common in HER2+ MBC. However, it remains unanswered whether the high frequency of BMs is merely related to the aggressiveness of HER2+ disease. Nevertheless, the observation is very relevant, and novel agents more efficient at penetrating the CNS to prevent or treat CNS metastases are urgently needed. It has been suggested that lapatinib may decrease the risk of developing CNS metastases. In a preclinical study by Palmieri et al. [18], lapatinib was reported to inhibit the formation of metastases in HER2+ human breast carcinoma cells. In accordance with this observation, several studies have reported efficacy of LC combination treatment in this patient population [13–17].

Table 5. Literature review of lapatinib use in patients with brain metastases from breast cancer

Study [ref.]	Regimen	n	ORR, %	PFS, months	OS, months
Lin et al. 2008 [12]	lapatinib	39	2.6	3.0 (TTP)	6.5
Boccardo et al. 2008 [13]	lapatinib + capecitabine	138	18.0	NR	NR
Lin et al. 2009 [14]	lapatinib	237	6.0	2.4	6.3
Lin et al. 2009 [14]	lapatinib + capecitabine	50	20.0	3.65	NR
Sutherland et al. 2010 [15]	lapatinib + capecitabine	34	21.0	5.2 (TTP)	NR
Metro et al. 2011 [16]	lapatinib + capecitabine	30	31.8	5.6	11
Bachelot et al. 2011 [17]	lapatinib + capecitabine	45	67.0	5.5 (TTP)	NR
Our study	lapatinib + capecitabine	85	27.1	7.0	13

ORR = Overall response rate; PFS = progression-free survival; OS = overall survival; TTP = time to progression; NR = not reported.

In a phase III study evaluating capecitabine versus LC therapy in MBC patients, the addition of lapatinib was shown to be associated with a reduced incidence of BMs as the first site of relapse, which has been considered as a preventive effect [9, 11]. Lapatinib has also been suggested to be administered concurrently with cranial radiotherapy, due to the preclinical data indicating that lapatinib may act as a radiosensitizer [19].

Selected studies of systemic therapy with lapatinib for BMs from HER2+ MBC are summarized in table 5 [12–17]. A total of 6 studies were reviewed. All but 1 study used capecitabine in addition to single-agent lapatinib. 2 studies were retrospective subgroup evaluations of the Lapatinib Expanded Access Program [13, 15], and 1 study was a retrospective analysis from Italy [16]. The remaining 2 reports were prospective phase II trials [14, 17]. Notably, the Landscape trial including 45 patients with BMs from HER2+ MBC involved the use of LC in the first-line treatment before WBRT [17]. The authors reported a stunning 67% ORR with a time to progression (TTP) of 5.5 months. The only phase II study using LC after WBRT reported a 20% ORR with a PFS of 3.65 months [14]. OS duration is generally lacking in all these studies except for the retrospective Italian study [16] which reported 11 months of OS, very similar to our finding. Overall, these studies reported ORRs in the range of 18–67%, and DFS or TTP of 3.65–5.6 months. Our results including a 27.1% ORR, 7-month PFS, and 13-month OS are in accordance with these reports indicating efficacy of LC in these patients. The most frequent adverse events were hand-foot syndrome, nausea, and fatigue. Most events were mild and resolved without the need for dose modification. Notably, cardiac side effects were absent. The LC combination was well-tolerated with an acceptable side effect profile.

In conclusion, modern therapies with better efficacy have led to a change in the prevalence and clinical significance of BMs from HER2+ MBC. The current standard of care in these patients still comprises WBRT and other local modalities such as stereotactic radiosurgery or conventional neurosurgery for oligometastases. Because trastuzumab is relatively ineffective in BMs, the most promising systemic treatment after WBRT appears to be LC combination therapy after progression on trastuzumab. However, clinical experience with lapatinib in this setting is limited, and more effective novel modalities are urgently required for BMs from HER2+ MBC.

Disclosure Statement

There is no conflict of interest.

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