Original Article

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Prognostic Factors Influencing Progression-Free Survival in HER2-Positive Metastatic Breast Cancer Patients Who Were Treated With A Combination of Lapatinib and Capecitabine

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ABSTRACT

Objective: The aim was to assess the prognostic variables in human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer patients receiving lapatinib plus capecitabine.

Materials and Methods: Retrospective data on HER2-positive metastatic breast cancer patients who received lapatinib and capecitabine were analyzed. Survival outcome was obtained with Cox regression analysis and the Kaplan–Meier method.

Results: The study included 102 patients. Forty-four (43.1%) patients had *de novo* metastatic disease. The most frequent metastatic sites were, in order, bone (61.8%), brain (57.8%), liver (35.3%), and lung (34.3%). All of the patients had previously received chemotherapy based on trastuzumab. With combined lapatinib and capecitabine, complete response was observed in 7.8%, partial response in 30.4%, and stable disease in 24.5%. Progression-free survival was 8 (95% confidence interval, 5.1–10.8) months. In multivariable analysis, endocrine therapy (p = 0.02), de novo metastatic disease (p = 0.02), and age (p = 0.02) were prognostic factors for progression-free survival. However, the number of chemotherapy cycles with trastuzumab, palliative radiotherapy, history of breast surgery, and the number of metastatic sites were not significant in this respect.

Conclusion: These results have demonstrated the effectiveness of lapatinib plus capecitabine in metastatic HER2-positive breast cancer patients. Furthermore, unfavorable prognostic factors for progression-free survival were shown to be hormone-negative tumor, *de novo* metastatic disease, and young age.

Keywords: Breast cancer; metastasis; HER2/neu receptor; lapatinib; capecitabine

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Key Points

- The combination of lapatinib and capecitabine was effective in the treatment of human epidermal growth factor receptor 2 positive metastatic breast cancer.
- Clinical and pathological factors affected the efficacy of the combination of lapatinib and capecitabine.
- The combination of lapatinib and capecitabine was well tolerated in patients and side effects are generally easily managed.

Introduction

Breast cancer is the most common malignancy in women globally and the second most frequent cause of cancer-related death (1). Breast cancer is divided into subtypes with biologically different characteristics. Human epidermal growth factor receptor 2 (HER2) oncogene receptor can be detected in approximately 15–25% of breast cancer patients (2, 3). The HER2 receptor is a transmembrane protein with intracellular tyrosine kinase activity from the epidermal growth factor receptor family (4). It has functions in cell growth and differentiation. HER2 receptor positivity is detected by *in situ* hybridization and immunohistochemistry (IHC) methods. Many therapeutic agents target the HER2 receptor, such as trastuzumab, pertuzumab, lapatinib, trastuzumab emtansine, and trastuzumab deruxtecan, and have been using to treat many HER2-positive solid tumors, especially breast and gastric cancer.

Trastuzumab is the first agent to used as a targeted therapy in the treatment of HER2-positive metastatic breast cancer patients. In patients whose disease progressed after trastuzumab-based therapy,

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tumor progression was delayed, and a trend towards an improvement in overall survival (OS) was achieved, although not statistically significant, with the combination of lapatinib plus capecitabine (LC) compared to only capecitabine (5, 6). In another study, the combination of LC was found to be superior in terms of progression-free survival (PFS) compared to capecitabine alone in patients who had previously received multiple treatments (anthracycline, taxane, and trastuzumab) (7). There is a limited number of studies examining the factors affecting the time to progression with the combination of LC in HER2-positive metastatic breast cancer patients who have received previous treatment. The aim of this study was to examine the factors affecting the efficacy of the combination of LC.

Materials and Methods

Patient Inclusion and Data

This study was designed as a cross-sectional, retrospective study. Ethics committee approval was obtained before the study, and our study was conducted according to good clinical practices guidelines. Patients who received treatment in a single oncology center between 2009 and 2020 were included in the study. The patients in the study were identified through the information processing system. All patients included in the study had metastatic breast cancer with HER2-positive features and had previously received at least one series of cancer chemotherapy. Patients who received other treatments, such as pertuzumab and trastuzumab emtansine targeting the HER2 receptor, other than trastuzumab-based treatment, before LC treatment, and patients who did not have sufficient data were excluded from the study. Demographic and clinicopathological features of the study cohort were extracted from hospital files. All treatments (surgery, radiotherapy, systemic cancer treatments) given to the patients were also noted. Progesterone receptor and estrogen receptor (ER) positivity were determined by IHC. HER2 receptor positivity was diagnosed by IHC (score 3) or *in situ* hybridization methods.

The patients used capecitabine 1000 mg/m^2 twice a day (1–14 days every three weeks) and lapatinib 1250 mg/day. Treatment-related response assessments were performed radiologically (computed tomography or magnetic resonance imaging) every three months. LC combination-related response assessment was performed using Response Evaluation Criteria in Solid Tumors (RECIST 1.1) criteria. In addition, treatment-related adverse events were graded. Records of patient deaths were extracted from the death information system of the Ministry of Health. OS was calculated as the duration from the onset of LC to death from any cause. PFS was determined as the duration from the beginning of LC to disease progression. Univariate and multivariate analyzes were performed for clinical and pathological parameters affecting PFS.

Statistical Analysis

Statistical analyzes were conducted with SPSS, version 25 (IBM Inc., Armonk, NY, USA). Continuous variables are shown as median values (minimum-maximum), while categorical variables are shown as numbers and percentages. Univariate analysis was performed for parameters affecting PFS. Multivariate analysis was done using the Cox regression method, using the parameters that were significant in the univariate analysis and the factors that were reported to have significance in the literature. Overlapping parameters were not included in the analysis. Survival curves were plotted with the Kaplan–Meier analysis. Statistical significance was assumed when $p<0.05$.

Results

Patients Characteristic and Treatment Modality

One hundred and nineteen HER2-positive metastatic breast cancer patients who had received LC were identified. Seventeen patients were excluded from the study because they had received trastuzumab emtansine or pertuzumab prior to LC treatment, and thus the data of 102 patients were analyzed. The median age of the patients included in the study was 47 (range 24–87) years, and three (2.9%) patients were male. The major histopathological subtype was invasive ductal carcinoma (76.5%), and ER positivity was present in 42.2% of the patients. At the time of diagnosis, 44 (43.2%) patients had *de novo* metastatic disease. The median number of metastatic sites was 4 (1–5). The most common site of metastasis was bone (61.8%), and 57.8% of patients had brain metastases. Table 1 presents the clinical and pathological features of the patients.

Mastectomy was performed in 61 (59.8%) patients. All of the patients received trastuzumab-based treatment before LC treatment. Before LC treatment, 54 (52.9%) of the patients had received one cycle of chemotherapy, and 48 (47.1%) had received two or more cycles chemotherapy regimens. The patients used chemotherapy regimens containing anthracycline, taxane, platinum, and fluoropyrimidine in different combinations as chemotherapy. Palliative metastasectomy for brain metastasis was performed in 11 (10.8%) patients. The number of patients who received palliative radiotherapy before treatment was 79 (77.5%), and 55 (53.9%) of these patients received brain radiotherapy. Fifty-five (53.9%) patients were given bisphosphonate therapy for bone metastases. The treatment features of the patients are presented in Table 2.

With LC chemotherapy, the overall response rate was 38.2%, and the disease control rate was 62.7% (Table 3). LC-related grade 1–2 adverse events were observed in 55 (57.3%) patients, and grade 3–4 adverse events were observed in 22 (22.9%) patients. The most common toxicities were non-hematological (fatigue, diarrhea, hand-foot syndrome, and others) and were observed in 57.8% of the patients. LC had to be discontinued in four (3.9%) patients due to toxicity. The most important toxicity leading to drug discontinuation was hand-foot syndrome. After LC treatment, 45 (44.1%) patients received palliative chemotherapy, and 19 (18.6%) patients received palliative radiotherapy.

Survival Outcomes and Prognosis

The median follow-up time after initiation of LC was 16.9 (1–149) months. During the study period, 91 (89.1%) patients died. The median PFS duration was 8 [95% confidence interval (CI), 5.1–10.8] months (Figure 1). Median OS was 17.8 (95% CI, 13.1–22.4) months (Figure 2). In the multivariate analysis for parameters affecting PFS, age (p = 0.02), *de novo* metastatic disease (p = 0.02), and use of palliative endocrine therapy (p = 0.02) were significant factors affecting PFS (Table 4). Primary tumor site, primary tumor surgery, histopathological type, number of metastasis sites, metastasis sites, number of palliative chemotherapy, and palliative radiotherapy were not found to be prognostic.

Discussion and Conclusion

These results suggest that LC was effective and safe for HER2-positive metastatic breast cancer patients who were previously treated. The combination of tyrosine kinase inhibitors such as lapatinib, pyrotinib,

Table 1. Clinical and pathological characteristics of the patients

	Number of patients (n = 102)	(%)
Age at diagnosis, years		
<50	55	53.9
≥50	47	46.1
Gender		
Female	99	97.1
Male	3	2.9
Number of metastatic sites		
1-2	55	53.9
≥3	46	45.1
Unknown	1	1
Metastatic sites		
Bone	63	61.8
Brain	59	57.8
Liver	36	35.3
Lung	35	34.3
Other sites		
Stage at diagnosis		
Stage 1	4	3.9
Stage 2	5	4.9
Stage 3	49	48
Stage 4	44	43.2
Primary tumor locations		
Left sides	49	48
Right sides	47	46.1
Bilateral	1	1
Unknown	5	4.9
Histological type		
Invasive ductal carcinoma	78	76.5
Other types	9	8.8
Unknown	15	24.7
ER status		
Positive	43	42.2
Negative	59	57.8
PR status		
Positive	33	32.4
Negative	69	67.6

ER: estrogen receptor; PR: progesterone receptor

Table 2. Treatment features of the patients

	Number of patients	%
Surgery		
Mastectomy	61	59.8
Lumpectomy	12	11.8
No	29	28.4
Radiotherapy before metastatic disease		
Adjuvant	38	37.3
Neoadjuvant	3	2.9
No	61	59.8
Chemotherapy before metastatic disease		
Adjuvant	41	40.2
Neoadjuvant	14	13.7
No	47	46.1
Endocrine therapy before metastatic disease		
Tamoxifen	20	19.6
Aromatase inhibitors	3	2.9
No	79	77.5
Palliative chemotherapy before LC		
1 series	54	52.9
≥2 series	48	47.1
Palliative endocrine therapy before LC		
Aromatase inhibitors	28	27.5
Tamoxifen	17	16.6
No	57	55.9
Palliative radiotherapy before LC		
Yes	79	77.5
No	23	22.5
Metastasectomy		
Yes	12	11.8
No	90	80.2

LC: lapatinib plus capecitabine

and neratinib with capecitabine is used in the treatment of HER2-positive metastatic breast cancer patients. Lapatinib selectively inhibits epidermal growth factor receptor and HER-2 tyrosine kinases and inhibits cell proliferation by restricting HER-2, AKT, Raf, and ERK phosphorylation, especially in breast cancer cells with high HER2 expression (8). In the study performed by Geyer et al. (7), the median time to progression with LC was 8.4 months in HER2-positive metastatic breast cancer patients who were previously treated, and it was superior to patients who received only capecitabine. In another study, inluding brain metastatic patients with HER2 positive breast cancer, conducted by Metro et al. (9), the disease control rate was 59%, and brain-specific progression survival was 5.6 months with LC combination. Similarly, in a meta-analysis that included 12 studies, the objective response with LC was 29%, while the median PFS was 4.1 months and the median OS 11.2 months (10). In a study comparing the combinations of lapatinib with capecitabine, vinorelbine, and gemcitabine, although it was not statistically significant, PFS was nine months with capecitabine and seven months with other agents, and the toxicity profiles of different agents were similar (11). It has been shown that the combination of LC passes into brain tissue in HER2-positive brain metastatic breast cancer patients who have not

Table 3. Responses to LC in the patients

	Number of patients (n = 102)	%	Actual-%
Response rates			
Complete response	8	7.8	8.3
Partial response	31	30.4	31.9
Stable disease	25	24.5	25.7
Progression	33	32.4	34.1
Overall response rate	39	38.2	40.2
Disease control rate	64	62.7	65.9
Unknown	5	4.9	

LC: lapatinib plus capecitabine

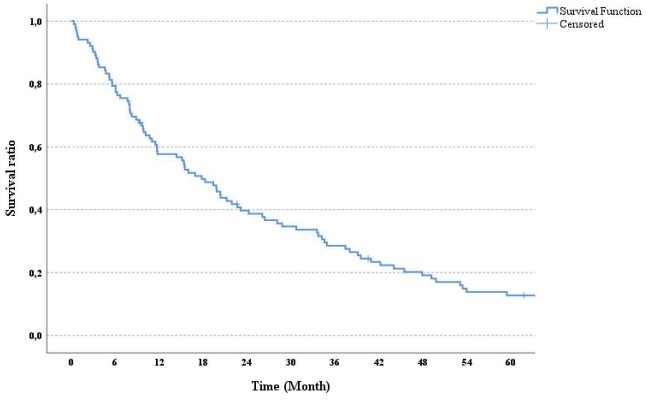

Figure 1. Kaplan–Meier Curve for PFS in the patients who were treated with LC

PFS: progression-free survival; LC: lapatinib plus capecitabine

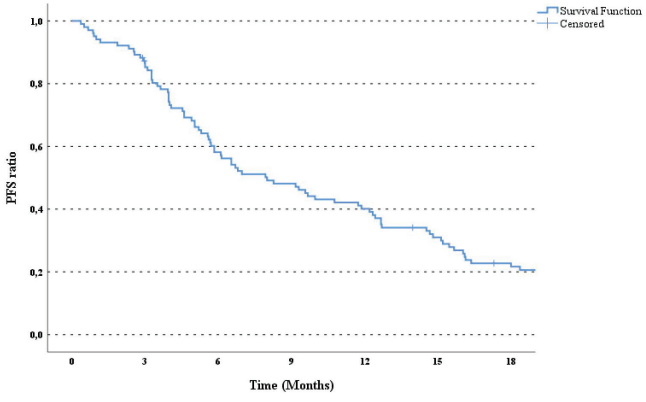

Figure 2. Kaplan–Meier curve for OS in the patients who were treated with LC

OS: overall survival; LC: lapatinib plus capecitabine

received brain radiotherapy (12). Therefore, LC treatment can be considered as an option to delay whole brain irradiation and its side effects in brain metastatic patients with HER2-positive breast cancer (13). In addition, in a case report, the combination of LC was shown to have efficacy in a breast cancer patient with leptomeningeal metastasis (14). Real-world data published by Gui et al. (15) showed that early initiation with lapatinib-based therapy was more beneficial in terms of PFS and OS. In this study, when lapatinib-based therapy was used in the first series, PFS was 10.4 months and OS 32.9 months, while in the third series, PFS was 5.8 months and OS 13 months. In the present study, half of the patients had brain metastases, and the results of LC-related survival results were consistent with the literature. In a study evaluating tucatinib, a new generation tyrosine kinase inhibitor, the addition of tucatinib to trastuzumab and capecitabine improved survival compared to placebo in patients with previously treated HER2-positive metastatic breast cancer (16). In addition, in patients with HER2 positive brain metastatic breast cancer, tucatinib provided better HER2 inhibition in both impaired and intact blood-brain barrier than neratinib and lapatinib (17). A meta-analysis showed that tucatinib in combination with trastuzumab + capecitabine or TDM-1 had better survival outcomes than lapatinib

Table 4. Univariate and multivariate analysis for PFS in the patients who were treated with LC

	Univariate analysis	Multivariate analysis	
	p	*p*	Odds ratio CI 95%
Age (<50 *vs.* ≥50)	0.06	0.02	0.57 (0.36–0.91)
***De novo* metastasis** (No *vs.* yes)	0.36	0.02	1.91 (1.07–3.40)
Primary tumor sites (Left *vs.* right)	0.34		
Primary surgery (No *vs.* Yes)	0.6	0.06	1.95 (0.97–3.94)
Histopathologival type (IDC *vs.* other type)	0.54		
ER status (Positive vs. negative)	0.36		
Number of metastatic sites (1-2 *vs.* ≥3)	0.53	0.24	
Brain metastasis (Yes *vs.* No)	0.99		
Liver metastasis (Yes *vs.* No)	0.28		
Lung metastasis (Yes *vs.* No)	0.72		
Number of palliative chemotherapy (1 *vs.* ≥2)	0.69	0.33	
Palliative hormonotheray (No *vs.* Yes)	0.15	0.02	0.58 (0.37–0.91)
Palliative radiotherapy (No *vs.* Yes)	0.91	0.39	

Hosmer and Lemeshow test model *p* value = 0.5, PFS: progression-free survival; LC: lapatinib plus capecitabine; CI: confidence interval; IDC: invasive ductal carcinomas; ER: estrogen receptor

+ capecitabine or other treatments in patients with metastatic breast cancer who received HER2-based therapy (18).

We observed that LC treatment response appeared to have different efficacy in different patients and different effects on PFS. There are limited studies in the literature predicting LC response. We found that patients under 50 years of age, *de novo* metastatic disease, and patients who do not receive palliative hormone therapy due to having hormone receptor-negative tumors had a worse prognosis in terms of PFS. In a study evaluating 52 HER2-positive metastatic breast cancer patients who received LC, time to progression was evaluated and those over 50 years of age, with hormone-positive disease, and with tumors with high HER2 and HER3 expression had better outcomes. Also, in this study, it was also determined that the absence of previous use of capecitabine and the high expression of HER2 and HER3 affected OS positively (19). In another study published by Ang et al. (20), it was reported that OS was significantly improved in patients who developed dermatitis and hand-foot syndrome within 42 days of the start of LC. This study also showed that nausea and vomiting as early side effects were associated with worse OS. In the analysis performed by Gui et al. (15), it was shown that liver metastasis, brain metastasis, number of metastatic sites, and hormone receptor status did not affect median PFS, but the use of LC combined and in early cycles significantly affected PFS in the patients receiving LC. The patient group included in this study was extremely heterogeneous, the 102 patients involved in the study were divided into three different groups, and many patients had previously used capecitabine as a single agent. In addition, some of the patients used different chemotherapy agents other than capecitabine together with lapatinib. In an open-label study published by Ro et al. (21), it was found that the presence of non-visceral metastatic disease and history of longer use of trastuzumab were associated with prolonged PFS in patients receiving LC combination. In this study, it was also detected that hormone receptor positivity and clinical benefit rate significantly increased for brain PFS.

Study Limitations

Our study had some limitations due to its retrospective nature. The patient group involved in the study was heterogeneous, and the number of patients was relatively limited. Some data of a small number of patients could not be collected.

In this study, we showed that LC was effective and safe in HER2-positive metastatic breast cancer patients who were previously treated. The LC-related prognostic factors were found to be associated with age, using endocrine therapy, and *de novo* metastatic disease. There is very limited research into the parameters that affect LC-related response. Our study contributes to the literature in this respect. In the future, there is a need for molecular and genetic studies that investigate factors affecting HER2-based treatment response in the treatment of breast cancer patients.

Ethics Committee Approval: The local ethics committee approved this study at the Istanbul University Faculty of Medicine (date/approval number: 28.06.2021/265629).

Informed Consent: Retrospective study.

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: İ.D., N.P., N.A., S.V., P.S., A.A.; Concept: İ.D., N.P., N.A., S.V., P.S., A.A.; Design: İ.D., N.P., N.A., S.V., P.S., A.A.; Data Collection or Processing: İ.D., N.P., N.A., A.A.; Analysis or Interpretation: İ.D., N.P., N.A., A.A.; Literature Search: İ.D., N.P., N.A., A.A.; Writing: İ.D., N.P., N.A., A.A.

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