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ORIGINAL ARTICLE

Duration of anti-HER2 blockage therapy may improve survival in HER2 positive metastatic breast carcinoma patients

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Summary

Purpose: *The duration of anti-HER2 blockage therapy in metastatic breast cancer patients is still unclear. We aimed to evaluate the effect of the anti-HER2 blockage therapy duration and other factors on survival in HER2 positive metastatic breast carcinoma (MBC) patients.*

Methods: *The medical records of 193 HER2 positive MBC patients, who did not have the opportunity to receive adjuvant trastuzumab therapy but had received trastuzumab in the metastatic setting were retrospectively evaluated.*

Results: *The median age at diagnosis was 45.0 years (range 21-83). Ninety-two (47.7%) patients received palliative trastuzumab < 6 months median, whereas 101 patients received trastuzumab ≥ 6 months median. The median number of trastuzumab cycles was 8 (range 1-51). Median survival after breast cancer recurrence was 31.0 months (range 24.3-37.7). The duration of trastuzumab therapy had a significant impact on the prognosis of recurrent breast cancer (22.0 vs 49.0 months, for ≤ 6 months of treatment duration, respectively; p<0.0001). Survival after breast cancer recurrence for the patients who received lapatinib plus capecitabine vs those who did not was significantly different (59 patients, p=0.005). Moreover, there was a statistically significant relationship between prolonged lapatinib plus capecitabine combination therapy and improved survival after disease recurrence (p=0.022). In the multivariate Cox regression analysis, treatment with trastuzumab > 6 months (p=0.003) was the only independent prognostic factor for survival after breast cancer recurrence.*

Conclusion: *The duration of anti-HER2 blockage therapies, especially with trastuzumab, seems to improve survival of HER2-positive metastatic breast cancer patients who were not previously treated with adjuvant trastuzumab, regardless of other therapies.*

Key words: *breast cancer, HER2 positivity, trastuzumab, survival*

Introduction

MBC is currently considered an incurable disease, but significant improvement in prognosis has been observed over the last decades [1]. Prolonged survival in MBC can be partly attributed to the discovery of new targeted agents against human epidermal growth factor receptor 2 (HER2).

Trastuzumab is a humanized monoclonal antibody of the immunoglobulin G1 type, which has been developed to target the HER2 in breast cancer [2]. Routine clinical use of trastuzumab has dramatically changed the prognosis of HER2 positive MBC, which is known for its aggressive clinical course [3-7]. However, most patients eventually progress, either from loss of effectiveness of trastuzumab on the HER2 receptor or a change in the intracellular HER2 pathway [8-10]. There are two possible options for the treatment of MBC; first, continuation of trastuzumab with a change of the cytotoxic partner, and second, switching to lapatinib combination therapies. Retrospective studies investigating the survival benefit of continuation of trastuzumab therapy beyond progres-

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sion have reported conflicting results [11-15]. In a prospective phase III trial, which was closed early because of the announcement of positive results of the combination of lapatinib with capecitabine [16], 156 MBC patients who progressed during trastuzumab treatment were randomly assigned to capecitabine alone or to continuation of trastuzumab therapy (6 mg/kg every 3 weeks). Continuation of trastuzumab was reported to be associated with a significantly longer median time to progression (8.2 vs 5.6 months) and a statistically non-significant improvement in overall survival (25.5 vs 20.4 months) [17].

Despite increasing knowledge regarding anti-HER2 therapies, the duration of anti-HER2 blockage therapy after disease progression that is required for a better outcome is still unclear. In our study, we aimed to evaluate the factors possibly affecting survival after the development of metastasis in trastuzumab or lapatinib naive HER2 positive MBC patients.

Methods

Patients for this analysis were selected retrospectively from the medical records of breast cancer patients with HER2 positive metastatic disease who did not have the opportunity to receive trastuzumab therapy on an adjuvant basis and who were treated between 1994-2009 in the Medical Oncology Clinics of two hospitals in Ankara. HER2-positivity was defined as a 3+ score by immunohistochemistry (IHC) in the primary tumor or biopsy specimen of metastatic tissue if available. Fluorescent *in situ* hybridization (FISH) or silver *in situ* hybridization (SISH) were used for all score 2+ tumors by IHC. Hormone receptor and HER2 status were assessed by the pathologists of each of the tertiary hospitals referring patients to our Medical Oncology Clinics after breast surgery. Estrogen receptor (ER) and progesterone receptor (PgR) status were determined by IHC. ER status was available for 184 patients and PgR status for 181 patients. Clinical characteristics, treatment schedules and survival data were evaluated in patients with HER2 positive MBC.

Statistics

Overall survival (OS) was calculated from the date of diagnosis to death for any reason or the date of last contact. Survival after breast cancer recurrence was accepted as the time from the day of metastasis till death or last contact. Progression free survival (PFS) was calculated from the date of first treatment until disease progression. Fisher's exact test was used to compare patient characteristics and tumor factors between the populations. The survival of patients was estimated using the Kaplan-Meier method. Log-rank test was used to compare and analyse the survival data. Determination of independent prognostic factors influencing survival was performed by the Cox proportional hazard model. The 95% confidence interval was calculated for all hazard ratios (HRs) in Cox regression analysis. A p value < 0.05 was considered to be statistically significant. For stastistical analysis, SPSS for Windows, version 15.0 software (SPSS Inc, Chicago, Illinois, USA) was used.

Results

Patient characteristics

A total of 193 women with HER2 positive MBC from two cancer centers who did not receive adjuvant trastuzumab therapy but received trastuzumab in the metastatic setting were enrolled in this study. Median age was 45 years (range 21-83). One hundred and nineteen (62%) patients were premenopausal and 90% were ER positive. The majority of the patients had locally advanced or metastatic disease at the time of diagnosis (54.4% stage III, 16.6% stage IV). Patients were categorized into 2 groups: those who received trastuzumab < 6 months (group A) and ≥6 months (group B) in the metastatic setting. Details of patient characteristics are shown in Table 1.

Thirty-six patients (18.7%) did not have any breast surgery. As an adjuvant therapy, 63 (32.6%) patients had received anthracycline - and 74 (38.3%) taxane-based chemotherapy. Forty-seven patients (24.4%) received no adjuvant chemotherapy and 88 (45.6%) received hormonotherapy. One hundred and eleven patients (57.5%) received adjuvant radiotherapy. The median cycles of adjuvant chemotherapy was 6.0 (range 1-10). Bone-soft tissue metastasis, visceral and multiple metastatic regions as the first site of metastasis were found in 64 (33.1%), 58 (30.1%) and 39 (19.7%) patients, respectively. Detailed information regarding the adjuvant treatment and first site(s) of metastasis for each group are listed in Table 2. Although central nervous system (CNS) was not the most common initial site of metastatic involvement, 65 patients (33.7%) developed brain metastasis during the follow-up period (35 patients in the trastuzumab <6 months group and 30 in the trastuzumab ≥ 6 months group,p=0.22).

Treatment in the metastatic setting

All of the 193 patients were treated with trastuzumab containing regimens in the metastatic setting. The schema of the study popula-

Table 1. Basic characteristics of patients according to duration of trastuzumab treatment

Characteristics	*Total*	*Trastuzumab ≥6 months*	*Trastuzumab <6 months*	*p-value*
	N (%)	*N (%)*	*N (%)*	
Median age, years (range)	45 (21-83)	44 (21-65)	46 (25-83)	0.45
Menopausal status				0.30
Premenopausal	119 (61.7)	66 (65.3)	53 (57.6)	
Postmenopausal	74 (38.3)	35 (34.7)	39 (42.4)	
Histology				0.90
Invasive ductal	182 (94.3)	94 (93.1)	88 (95.7)	
Invasive lobular	2 (1.0)	1 (1.0)	1 (1.1)	
Other	9 (4.7)	6 (5.9)	3 (3.2)	
Grade				0.23
I	4 (2.1)	1 (1.0)	3 (3.2)	
II	50 (25.9)	30 (29.7)	20 (21.7)	
III	75 (38.9)	41 (40.6)	34 (36.9)	
Unspecified	64 (33.1)	29 (28.7)	35 (38.0)	
Stage				0.15
I	4 (2.1)	3 (3.0)	1 (1.1)	
II	40 (20.7)	25 (24.8)	15 (16.3)	
III	105 (54.4)	48 (47.5)	57 (62.0)	
IV	32 (16.6)	21 (20.8)	11 (12.0)	
Unknown	12 (6.2)	4 (4.0)	8 (8.7)	
Estrogen receptor				0.30
Positive	90 (46.6)	47 (46.5)	43 (46.7)	
Negative	94 (48.7)	52 (51.5)	42 (45.7)	
Unknown	9 (4.7)	2 (2.0)	7 (7.6)	
Progesterone receptor				0.15
Positive	91 (47.2)	52 (51.5)	39 (42.4)	
Negative	90 (46.6)	47 (46.5)	43 (46.7)	
Unknown	12 (6.2)	2 (2.0)	10 (10.9)	
HER2				0.83
3+	182 (94.3)	96 (95.0)	86 (93.4)	
2+	11 (5.7)	5 (5.0)	6 (6.5)	
FISH+	8 (4.1)	3 (3.0)	5 (5.4)	
SISH+	3 (1.6)	2 (2.0)	1 (1.1)	
Surgery				0.72
MRM	144 (74.6)	75 (74.3)	69 (75.0)	
Other	13 (6.7)	5 (5.0)	8 (8.7)	
No surgery	36 (18.7)	21 (20.8)	15 (16.3)	
Total	193 (100)	101 (100)	92 (100)	

MRM: modified radical mastectomy

tion according to treatment lines of trastuzumab is shown in Figure 1. In the first line, 68.9% (N=133) of the patients received trastuzumab together with taxane or vinorelbine (mostly taxane, N=109 and vinorelbine, N=19). Sixty-four (33.2%) patients were treated with a trastuzumab combination chemotherapy in the 2nd line (mostly taxane; N=43, and vinorelbine; N=21). The other 27 patients were given trastuzumab in the 3rd line and 10 patients in the 4th or 5th lines for their metastatic disease. As expected, the vast majority of patients who continued to receive trastuzumab beyond progression were in the group of trastuzumab ≥ 6 months (34 vs 5).

For all but 4 patients, a three-weekly trastuzumab regimen was used. Median time of the trastuzumab treatment was 6 months. Ninety-two (47.7%) patients received palliative trastuzumab for less than a median of 6 months, whereas 101 patients for more than or equal to 6 months. The median number of cycles of trastuzumab received was 8.0 (range 1-51). There were only 27 and 10 patients using trastuzumab in 3rd and subsequent lines. It is difficult to draw a precise conclusion about the effectiveness of trastuzumab therapy in such small sample sizes, but the results showed that PFS gradually decreased when trastuzumab therapy was given in subsequent lines (PFS according to the 1st, 2nd and 3rd or more treatment lines was 8, 6, 4.5 and 1.5 months, respectively; p< 0.0001) (Figure 2).

Fifty-nine (30.6%) patients were treated with

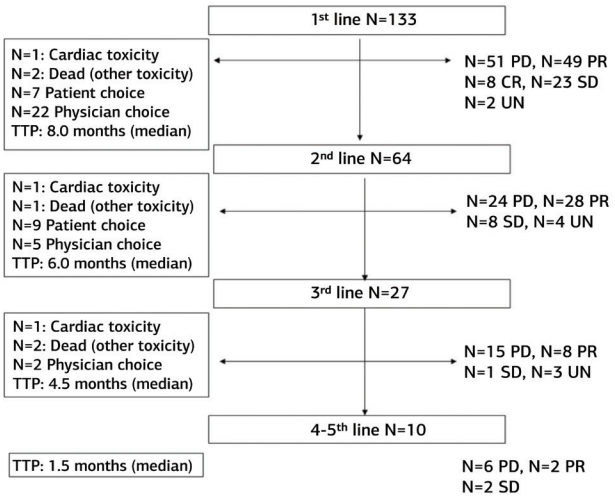

Figure 1. Schema of the study population according to treatment lines of trastuzumab. Reasons for trastuzumab cessation (left side) and known response status (right side). N: Number of patients, TTP: Time to progression, PD: Progressive disease, SD: Stable disease, PR: Partial response, CR: Complete response, UN: Unknown, missing data. 1st ,2nd, 3rd, 4-5th lines represent the line of chemotherapy.

lapatinib and capecitabine in the metastatic setting (13 in the 2nd line, 20 in the 3rd line, 18 in the 4th line, and 8 in the 5th line). The median number of lapatinib cycles was 6 (range 1-20).

Survival analysis

Median follow-up time was 40 months (range 3-284). At the time of survival analysis 108 patients had died because of progressive disease. Median survival after the development of metastatic disease was 31.0 months (range 24-37). Median survival times after metastatic disease according to the first site of metastasis were as follows: bone-soft tissue (49.0 months, range 21.3-76.7), visceral organ (28.0 months, range 22.7-33.3) and multiple sites (29.0 months, range 19.3-38.8) (p=0.004).

Survival after metastasis correlated with the duration of trastuzumab therapy (22.0 [95%CI 18.8-25.2] months vs 49.0 [95%CI 28.3-69.7] months for less than or longer than a median 6 months of duration, respectively, p<0.001, Figure 3). There was no statistically significant survival difference between trastuzumab use without progression (≥6 months) and beyond progression

Table 2. First site(s) of metastasis and adjuvant treatments received

	Total N (%)	*Trastuzumab ≥6 months* N (%)	*Trastuzumab <6 months* N (%)	*p-value*
First site of metastasis				
Bone	29 (18.1)	17 (20.7)	12 (15.4)	
Soft tissue	35 (21.9)	19 (23.2)	16 (20.5)	
Lung	29 (18.1)	13 (15.8)	16 (20.5)	0.25
Liver	24 (14.4)	12 (47.4)	12 (15.4)	
Brain	5 (3.1)	0 (0.0)	5 (6.4)	
Multiple	38 (23.8)	21 (25.6)	17 (21.8)	
Intitially diagnosed with metastatic disease				
Bone	5(16.7)	1 (1.0)	4 (36.4)	
Distant lymph node	1 (3.3)	0 (0.0)	1 (9.1)	
Lung	5 (16.7)	3 (15.8)	2 (18.2)	0.063
Liver	10 (33.3)	9 (47.4)	1 (9.1)	
Multiple	9 (30.0)	6 (31.8)	3 (27.3)	
Neoadjuvant and/or adjuvant therapy				
Anthracycline	63 (32.6)	32 (31.7)	31 (33.7)	
Anthracycline and taxane	74 (38.3)	39 (38.6)	35 (38.0)	
Other	9 (4.7)	2 (2.0)	7 (7.6)	
None	48 (24.4)	28 (27.7)	19 (20.7)	0.48
Radiotherapy	111 (57.5)	55 (55.4)	56 (60.9)	
Hormonotherapy	88 (45.6)	46 (45.5)	42 (45.7)	
Total	193 (100)	101 (100)	92 (100)	

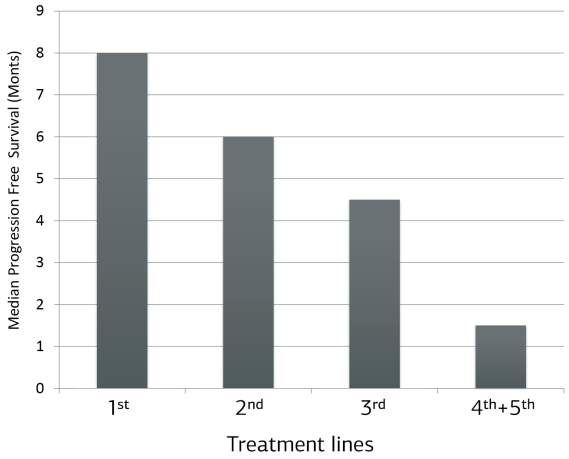

Figure 2. Median progression free survival after metastasis according to the 1st, 2nd, 3rd, 4th+5th treatment lines, respectively: 8.0, 6.0, 4.5 and 1.5 months (p<0.0001).

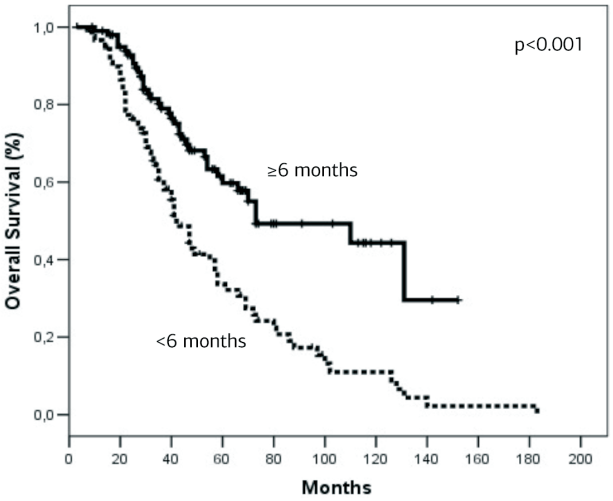

Figure 3. Kaplan-Meier survival curves showing overall survival after metastasis according to the duration of trastuzumab.

(≥6 months) (p=0.438). One-year, 2-year and 5-year survival rates after metastasis in patients who received trastuzumab ≥6 months were significantly longer than in patients treated with trastuzumab <6 months (90, 74 and 40% vs 77, 47 and 16%, respectively). One-year, 2-year and 5-year overall survival rates after metastasis according to the duration of trastuzumab therapy are shown in Table 3.

Survival after metastasis for the patients who received lapatinib plus capecitabine was also different as compared to those who did not receive this treatment (59 patients, log rank p=0.005). There was a statistically significant correlation between prolonged lapatinib combination therapy and improved survival after metastasis (p=0.022).

Table 3. One-year, 2-year and 5-year overall survival rate after metastasis according to duration of trastuzumab therapy

	Survival		
	Trastuzumab ≥6 months (%)	*Trastuzumab <6 months (%)*	*p-value*
1-year	90	77	
2-year	74	47	<0.0001
5-year	40	16	

If we grouped the patients into two further subsets, trastuzumab continuation (N=39) or those who did not continue with trastuzumab beyond disease progression (N=87), the first patient group showed a prolonged survival after metastasis: 37.0 months (95%CI 26.1-47.9) vs 22.0 months (95%CI 19.1-24.9), respectively (log rank p=0.008).

Survival after metastasis did not differ according to menopausal status (log rank p=0.366), ER positivity (log rank p=0.769), PgR positivity (log rank p=0.858), adjuvant hormonotherapy (log rank p=0.186) or adjuvant radiotherapy (log rank p=0.283) (Table 4).

Factors that affected survival after metastasis were included in the multivariate Cox regression analysis: stage at diagnosis (I-II vs III-VI), metastatic localization (bone and soft tissue vs visceral), treatment with trastuzumab longer than 6 months (≤6 months vs > 6), and lapatinib treatment (yes vs no). In multivariate Cox regression analysis, being treated with trastuzumab > 6 months (HR 0.41, 95% CI 0.22 – 0.73, p=0.003) was the only independent prognostic factor for OS after metastasis.

Discussion

This study showed that trastuzumab treatment longer than a median of 6 months in a metastatic setting significantly improved OS. Furthermore, survival after metastatic disease was significantly longer for the group that continued on trastuzumab after progression vs the group that stopped trastuzumab treatment upon progression.

We may also speculate that a comparison between patients who received trastuzumab for less than or greater than 6 months is reasonable. In the early trastuzumab era, contrary to our current knowledge, we treated HER2 positive patients with the logic that trastuzumab use is effective only together with chemotherapy in the treatment of MBC. Thus, trastuzumab treatment was terminated prematurely for various reasons, including chemotherapy cessation. Until 2008, before

Table 4. Factors related to overall survival after metastasis

Factors	*Median overall survival, months (95% CI)*	*p-value*
Total	31.0 (24.0-37.0)	-
Age (years)		
<45	34.0 (28.0-39.0)	0.355
≥45	27.0 (17.0-36.0)	
Menopausal status		
Premenopausal	30.0 (20.0-39.0)	0.366
Postmenopausal	34.0 (17.0-50.0)	
Grade		
I-II	30.0 (15.0-44.0)	0.379
III	31.0 (24.0-37.0)	
Stage at initial diagnosis		
I-II	47.0 (10.0-66.8)	0.005
III	26.0 (20.1-31.9)	
IV	26.0 (14.9-37.1)	
ER status		
Positive	29.0 (19.0-38.0)	0.769
Negative	35.0 (28.0-41.0)	
PgR status		
Positive	34.0 (24.0-37.0)	0.858
Negative	31.0 (23.0-44.0)	
Adjuvant chemotherapy		
Yes	35.0 (27.0-42.0)	0.283
No	22.0 (16.0-27.0)	
Adjuvant chemotherapy type		
Anthracycline	35.0 (20.0-49.0)	0.125
Taxane	28.0 (23.0-32.0)	
Other	46.0 (3.0-105.0)	
Adjuvant radiotherapy		
Yes	28.0 (23.0-32.0)	0.283
No	42.0 (30.0-53.0)	
Adjuvant hormonotherapy		
Yes	31.0 (23.0-38.0)	0.186
No	35.0 (22.0-47.0)	
Metastatic site		
Bone and soft tissue	49.0 (21.3-76.7)	0.004
Visceral	28.0 (22.7-33.3)	
Multiple	29.0 (19.3-38.8)	
Duration of trastuzumab treatment (months)		
<6	22.0 (18.8-25.2)	<0.001
≥6	49.0 (28.3-69.7)	
Trastuzumab use without progression (≥6 months)	110.0 (67.0-152.9)	0.048
vs beyond progression (≥6 months)	54.0 (28.4-79.8)	
Trastuzumab therapy		
First line	29.0 (23.9-34.1)	0.082
2nd and later lines	42.0 (24.3-37.7)	
Lapatinib therapy		
Yes	66.0 (26.5-105.5)	0.005
No	28.0 (22.1-33.9)	
Lapatinib therapy		
<6 cycles	29.0 (25.2-32.8)	0.022
≥6 cycles		

ER: estrogen receptor, PgR: progesterone receptor

widespread use of lapatinib after progression on trastuzumab, there was no other HER2 targeted therapy option except to continue on trastuzumab together with changing associated chemotherapeutic agents.

For MBC, the duration of trastuzumab usage is still an important issue, as it is for the optimal duration of chemotherapy. In a recent meta-analysis, the authors disclosed that prolonged duration of first-line cytotoxic treatment has provided a statistically significant advantage in PFS but a minimal benefit on OS compared with fewer cycles of chemotherapy in MBC [18]. The main mechanism of action of chemotherapy drugs is generally based on breaking the cell cycle at certain points, thus inhibiting cell proliferation and subsequently causing cells to undergo apoptosis [19]. However, although the exact mechanism of action of trastuzumab is not fully understood, there is strong evidence to suggest that its activity is considerably different from cytotoxic drugs [20].

In a preclinical model, Pietras et al. noted that tumor expansion started again soon after trastuzumab treatment ended. Therefore, trastuzumab has also been accepted as having a cytostatic effect [21]. But none of the randomized prospective phase III trials evaluating the effectiveness of a trastuzumab and chemotherapy combination in MBC included a short-term trastuzumab arm for comparison with a long-term trastuzumab arm. Although there is no data from randomized trials, unlike the practices of cytotoxic therapy in MBC, it makes sense to continue on trastuzumab, especially in responsive patients [22,23].

Whether to continue trastuzumab for patients who have progressive disease during treatment is still debatable. In an in vivo progressive disease model, it was demonstrated that trastuzumab monotherapy already culminates in antitumor activity during treatment, and trastuzumab efficacy was regained in combination with taxanes and capacitabine [24]. A review of recent data also supports the use of trastuzumab beyond progression in routine clinical practice [25]. In the final OS analysis of the GBG-26 study, Von Mickwitz et al. did not find a significant survival difference between patients treated with capecitabine alone and capecitabine plus trastuzumab after disease progression under trastuzumab treatment [17]. However, post-progression survival of patients who received anti-HER2 treatment as a third line therapy was better than in those who did not receive this targeted treatment [26]. In a large ob-

servational study subgroup analysis, Extra et al. demonstrated that trastuzumab treatment beyond progression provided a survival benefit as compared with patients who stopped trastuzumab after disease progression (p<0.001) [27]. Recently, Blackwell et al. also suggested a benefit for continuation of HER2 blockage after failure of trastuzumab in a randomized phase III trial (N=296, lapatinib vs lapatinib plus trastuzumab). Objective responses were similar but PFS was significantly longer with dual therapy (median 12 vs 8.4 months), and there was a non-statistically significant trend toward longer survival in this group (median 52 vs 39 weeks) [28].

The above mentioned clinical prospective data confirms the importance of maintaining trastuzumab therapy through disease progression into second- and subsequent treatment lines. Also, Tripathy et al. showed that continuation of trastuzumab beyond disease progression is safe and well-tolerated [29]. Moreover, our patients with trastuzumab use in the progression group (≥6 months) appeared to have similar survival compared with the group using trastuzumab without progression (≥6 months). Nevertheless, we cannot reach a firm conclusion about continuation of trastuzumab treatment beyond progression, whether it will always be equally effective compared to patients who continue to respond to trastuzumab treatment. Because of the retrospective characteristics of the data, we could not possibly provide a well-balanced distribution in terms of metastatic site, number of metastases, previous treatment lines, and hormone receptor positivity rate. The proportion of patients using granulocyte colony stimulating factor (G-CSF) may also differ between the two groups. One of the important underlying mechanisms of the antitumor activity of trastuzumab is an antibody-dependent cellular cytotoxicity that is based on the internalization and degradation of HER2 by tumor cells upon interaction with trastuzumab, thus hampering the usual activities of the HER2 receptor and blocking signal transduction cascades [20]. In preclinical models, it has been suggested that using G-CSF in addition to trastuzumab may provide a strong tumor growth inhibition associated with an increase in ADCC activity by enhancing FcγR expression in peripheral blood mononuclear cells [24,30]. Lastly, the patients with a relatively low tumor burden may predominantly accumulate in the group using trastuzumab with progression (≥6 months).

After 2008, lapatinib became available for MBC patients who progressed under trastuzumab treatment. Consequently, a group that was treated with lapatinib plus capecitabine was included during the latter time period of this study. In our previous study, due to the lack of an adequate follow-up period for patients who had been treated with lapatinib, we could not provide any further comment [31]. But now we have found a positive correlation between the duration of lapatinib plus capecitabine treatment and survival after metastasis in patients who progressed under trastuzumab therapy.

There is no data about short-term or extended use of lapatinib combination in MBC patients. A direct effect of lapatinib on CNS metastasis may be speculated. In a breast cancer xenograph model, Gril et al. showed that the development of CNS metastases, especially large ones, can be suppressed by lapatinib, but CNS metastasis cannot be prevented completely [32]. On the other hand, although less patients developed CNS metastasis in the combination arm, Geyer et al. did not find a significant difference between lapatinib plus capecitabine and capecitabine alone for the incidence of CNS metastasis as the first site of progression [16]. In the current study, half of the patients treated with lapatinib did not experience CNS recurrence, but we cannot reach a firm conclusion about the success of the combination in terms of preventing CNS metastasis. In contrast to the lapatinib arm, the remaining patients received a variety of chemo- and targeted- therapy regimens, including trastuzumab, antihormonal agents and various cytotoxic agents.

In addition, one-third of all patients developed CNS metastasis during follow-up and nearly half of those patients received lapatinib in combination with capecitabine soon after local treatment of the CNS. French and American investigators have separately reported encouraging results with a lapatinib combination on brain metastasis from breast cancer in recent studies [33,34].

More recently, Gori et al. retrospectively evaluated the clinical outcome of 69 patients with HER2 positive MBC treated with trastuzumab after lapatinib progression. Their results suggested that median OS was positively influenced by the continuation of anti-HER2 blockage therapy for patients experiencing clinical benefit (not reached vs 13.4 months for patients without clinical benefit; p = 0.002) [35].

Mechanisms of action of targeted therapies are quite complex and totally different from cytotoxic agents. Therefore, targeted therapies may continue to be useful at the stage of disease pro-

gression by changing the cytotoxic partner. As shown, the duration of both lapatinib and especially trastuzumab therapy seems to improve survival in HER2 positive MBC patients who were not previously treated with adjuvant trastuzumab, regardless of other chemotherapies.

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