Survival Outcomes of Retreatment with Trastuzumab and Cytotoxic Chemotherapy for HER2-Positive Recurrent Patients With Breast Cancer Who Had Been Treated with Neo/adjuvant Trastuzumab Plus Multidrug Chemotherapy: A Japanese Multicenter Observational Study

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ABSTRACT

BACKGROUND: There are little data on the usefulness of trastuzumab (TZM) retreatment as the first-line treatment for patients with HER2 (human epidermal growth factor receptor 2)–positive breast cancer recurrence after perioperative treatment with TZM.

AIM: To clarify the outcome and safety of TZM retreatment in patients with recurrent HER2-positive breast cancer.

METHOD: An observational study was conducted on patients who relapsed after primary systemic therapy with TZM using the central registration system. The primary end point was progression-free survival (PFS). Secondary end points consisted of the response rate, overall survival (OS), and safety.

RESULT: In total, 34 patients were registered between July 2009 and June 2012. The median follow-up time was 23.7 months (2-24 months). The 1- and 2-year PFS rates were 46.9% (95% confidence interval (95% CI): 29.2%-62.9%) and 29.8% (95% CI: 15.0%-46.3%), respectively (median 10.6 months). The median PFS time for patients receiving TZM combined with CTx was 13.9 months. The 1-and 2-year OR rates were 93.9 (95% CI: 77.9%-98.4%) and 84.8% (95% CI: 67.4%-93.4%). Trastuzumab-induced grade 3/4 adverse events were not observed.

CONCLUSIONS: This study suggests that the PFS and OS in Japanese patients who relapsed after perioperative TZM therapy improved or were similar to those in previous reports. Differences in patient backgrounds and treatments must be considered when interpreting the results. Trastuzumab should be used combination with CTx and/or HTx for retreatment. Retreatment with TZM is safe.

Trial registration: UMIN000002738.

KEYWORDS: breast cancer, HER2, metastatic/recurrence, trastuzumab, retreatment

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Introduction

In the 1980s, HER2 (human epidermal growth factor receptor 2) was identified as a prognostic factor.[1,2] Slamon et al[3] compared a group of HER2-positive patients with metastatic breast cancer (MBC) in whom only chemotherapy with paclitaxel or anthracycline and cyclophosphamide was performed as primary treatment with a group of patients in whom chemotherapy was combined with trastuzumab therapy, demonstrating the usefulness of trastuzumab. Since then, anti-HER2 therapy for HER2-positive metastatic/recurrent breast cancer, pertuzumab (CLEOPATRA study),[4] and T-DM1 (trastuzumab emtansine) (EMILIA study, TH3RESA study)[5,6] have been developed. These HER2-targeting agents markedly improved the outcome of HER2-positive advanced and recurrent breast cancer.

In the guidelines prepared by the ASCO (American Society of Clinical Oncology) and ESMO (European Society for Medical Oncology),[7,8] HER2-targeting regimens for HER2-positive advanced and recurrent breast cancer, such as pertuzumab + trastuzumab + taxans, and T-DM1 and trastuzumab combined with chemotherapy, are recommended.

However, there are countries and/or regions where pertuzumab or T-DM1 may not be used or are restricted. In such circumstances, trastuzumab and chemotherapy is inevitable as the first choice, but paucity of data is available on trastuzumab retreatment for patients with breast cancer who relapse after perioperative trastuzumab therapy.

The purpose of this observational study was to clarify the efficacy and safety of retreatment with trastuzumab for Japanese patients with recurrence after perioperative treatment with trastuzumab.

Patients and Study Design

Using the central registration system, a clinical observational study was conducted involving patients with HER2-positive breast cancer in whom recurrence was confirmed after perioperative treatment with trastuzumab for early breast cancer. Among the days of specimen collection for cytological or histological diagnosis and imaging procedures, the day on which recurrence was initially diagnosed was regarded as the day of recurrence.

Eligibility criteria consisted of (1) age on registration: 20 years or older, (2) trastuzumab administration for 10 months or more as perioperative treatment, (3) presence of evaluable lesions (measurable lesions are not essential), (4) left ventricular ejection fraction (LVEF) within 28 days before the start of treatment for recurrence: ≥50%, and (5) adequate Informed consent (IC). Exclusion criteria consisted of (1) stage IV patients at initial diagnosis or (2) presence of brain metastasis.

The study protocol was approved by each institutional review board. Data management was conducted by the Department of EBM Research, Institute for Advancement of Clinical and Translational Science, Kyoto University Hospital. The data were collected using an electronic data capture system (Satellite; Densuke Systems Co., Ltd., Tokyo, Japan). This study has been registered with the University Hospital Medical Information Network (UMIN000002738).

Primary and Secondary End Points

The primary end point in this study was progression-free survival (PFS). This refers to the interval from the first day of trastuzumab administration for recurrence until the confirmation of disease progression. In all registered patients, the earliest appearance of disease progression (include brain-only lesion), primary disease-related death, or other disease-related death was regarded as an event. In the other patients, the day on which the absence of disease progression was finally confirmed was regarded as the point of completion.

Secondary end points in this study included response rate, overall survival (OR), and safety. Tumor assessment was based on Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 with appropriate imaging study including computed tomography, magnetic resonance imaging, or other. The proportion of patients with complete response (CR) or partial response (PR) was regarded as the response rate. The interval from the first day of trastuzumab administration for recurrence until the day of death was regarded as OS. Events included death from any cause. In surviving patients and those in whom survival was unclear, the day of final survival confirmation was regarded as the point of completion. Regarding safety and adverse events, we adopted data on events that were considered to be related to trastuzumab by clinicians or of which the relationship with trastuzumab could not be ruled out. Safety was evaluated according to the NCI-Common Terminology Criteria for Adverse Events v4.0 (CTCAE v4.0) (Japanese version, JCOG version).

Statistics

All eligible patients were analyzed. For the background of the patient population, categorical variables were summarized with the frequency and rate and continuous variables with fundamental statistics. The PFS and OS were estimated using the Kaplan-Meier method. Similarly, the PFS was estimated in subgroups. Log-rank tests for time-to-event end points provided 2-sided P values, and P values $<.05$ were considered statistically significant. Cox regression analysis was used to estimate hazard ratios and 95% confidence intervals (CIs). For analysis, SAS software ver. 9.3 was used.

Results

Patient characteristics and treatment

A total of 34 patients were registered between July 2009 and June 2012. The mean age was 53.5 years. The median follow-up time was 23.7 months (2-24 months). The age at the time of recurrence, state of menopause, T and N stage, histologically invasive diameter, number of lymph node metastases at initial diagnosis, histological grade, HER2 status, estrogen

receptor (ER) status, progesterone receptor (PgR) status (priority order was defined as status at recurrence → that at the time of surgery → that at the initial diagnosis), interval from the resection of the primary lesion until recurrence (<12, 12-24, and ≥24 months), and site of recurrence are shown in Table 1.

There was no history of heart failure in any patient. Hypertension requiring treatment was noted in 3 patients (8.8%). All patients had received chemotherapy with anthracyclines, taxans, or both concurrently and sequentially combined with trastuzumab before and/or after surgery. Hormone therapy had been performed for all hormone receptor–positive patients as primary systemic treatment.

First-line treatment after recurrence is shown in Table 2. Trastuzumab monotherapy was performed for 2 patients (5.9%), trastuzumab + chemotherapy for 26 (76.5%), trastuzumab + hormone therapy for 4 (11.8%), and trastuzumab + chemotherapy + hormone therapy for 2 (5.9%). Trastuzumab was administered to 14 patients (41.2%) weekly and to 20 (58.8%) triweekly. For chemotherapy, taxans were administered to 17 patients (60.7%) and to 11 others (39.3%).

Response rate

For time to event analysis, patients with disease progression/death after 24 months were regarded as surviving patients without disease progression at 24 months. The best response was evaluated, and the response rate was calculated as the sum of CR and PR patients. The response rate (CR + PR) was 44.1% (CR: 9 patients, PR: 6 patients, stable disease [SD]: 12 patients, progressive disease [PD]: 5 patients, and not evaluable [NE]: 2 patients). The response rate stratified by treatment was 50% in combination with trastuzumab and chemotherapy and 100% in combination with trastuzumab, chemotherapy, and hormonal therapy as shown in Table 3.

Progression-free survival

In all patients, PFS was analyzed using the Kaplan-Meier method. The 1- and 2-year PFS rates were 46.9 (95% CI: 29.2%-62.9%) and 29.8% (95% CI: 15.0%-46.3%), respectively, with a median PFS period of 10.6 months (95% CI: 6.4-18.9 months) (Figure 1A). Progression-free survival, with respect to the subgroups age, state of menopause, T factor for the primary lesion, N factor, histological grade, HER2 status, ER, PgR, ER/PgR, surgical procedure, interval from the primary surgery until recurrence, site of recurrence (locoregional, sites other than locoregional), presence or absence of pre/postoperative chemotherapy, treatment for recurrence, type of chemotherapy for recurrence, and response to treatment, was analyzed. The log-rank test and Cox regression analysis with dummy variables were conducted. None of the variables reached significance but the use of chemotherapy combination with trastuzumab (Figure 1B). The median PFS of patients receiving trastuzumab and chemotherapy was 13.9 months.

Table 1. Patient characteristics.

Number		34	(100.0%)
Age (at diagnosis of recurrence)	Mean (SD)	53.5	(13.6)
	Min/max	25	77
Menopausal state	Pre	14	(41.2%)
	Post	20	(58.8%)
T	TX	1	(3.0%)
	T1	3	(9.1%)
	T2	20	(60.6%)
	T3	7	(21.2%)
	T4	2	(6.1%)
	N.A.	1	
N	NX	0	(0.0%)
	N0	7	(21.2%)
	N1	19	(57.6%)
	N2	5	(14.7%)
	N3	2	(6.1%)
	N.A.	1	
Histological grade	1	1	(3.0%)
	2	6	(18.2%)
	3	26	(78.8%)
	N.A.	1	
HER2 status	IHC ≤2/FISH+	3	(8.8%)
	IHC 3	30	(88.2%)
	IHC unknown/FISH+	1	(2.9%)
ER/PgR status	Either positive	18	(52.9%)
	Both negative	16	(47.1%)
From resection of primary tumor to recurrence	<12 mo	2	(5.9%)
	12-24 mo	11	(32.4%)
	>24 mo	21	(61.8%)
	Mean (SD)	32.0	(18.2)
	Max, min	7	98
Site of recurrence Multiple selection	Preserved breast, Ax	8	(23.5%)
	Chest wall, Sp, Ps	10	(29.4%)
	Counter side Ax	3	(8.8%)
	Liver	7	(20.6%)
	Lung	10	(29.4%)
	Bone	7	(20.6%)
	Other	8	(23.5%)
Disease type	Visceral	16	(47.1%)
	Nonvisceral	18	(52.9%)

Table 2. First-line treatment for recurrence in this study.

Number		34	(100.0%)
Combination with trastuzumab	Trastuzumab monotherapy	2	(5.9%)
	Trastuzumab + chemotherapy	26	(76.5%)
	Trastuzumab + hormonal therapy	4	(11.8%)
	Trastuzumab + chemotherapy + hormonal therapy	2	(5.9%)
Trastuzumab schedule	Weekly	14	(41.2%)
	Triweekly	20	(58.8%)
CTx	DTX	4	(14.3%)
	PTX	11	(39.3%)
	TC	2	(7.1%)
	Capecitabine	3	(10.7%)
	TS-1	2	(7.1%)
	VNR	6	(21.4%)
Hormonal therapy	TAM	1	(16.7%)
	LET	4	(66.7%)
	ANA + LH-RH	1	(16.7%)

Abbreviations: DTX, docetaxel; PTX, paclitaxel; TC, docetaxel/cyclophosphamide; VNR, vinorelbine; TAM, tamoxifen; LET, letrozole; ANA, anastrozole; LHRH, LHRH analogue.

Table 3. Response rate in this study.

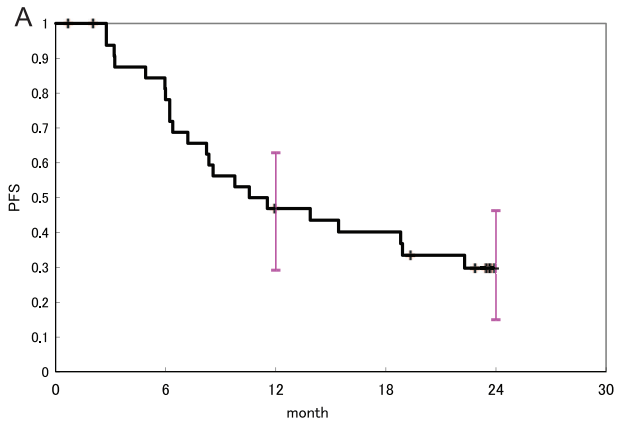
	Response	34	(100.0%)
Best response	CR	9	(26.5%)
	PR	6	(17.6%)
	SD	12	(35.3%)
	PD	5	(14.7%)
	NE	2	(5.9%)
Response rate			
All patients (n = 34)	CR/PR	9/6	(44.1%)
Trastuzumab + chemotherapy (n = 26)	CR/PR	8/5	(50.0%)
Trastuzumab + chemotherapy + hormonal therapy (n = 2)	CR/PR	1/1	(100.0%)
Trastuzumab + hormonal therapy (n = 4)	CR/PR	0/0	(0.0%)
Trastuzumab monotherapy (n = 2)	CR/PR	0/0	(0.0%)
Disease progression after first-line treatment	No	13	(38.2%)
	Yes	21	(61.8%)

Abbreviations: CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

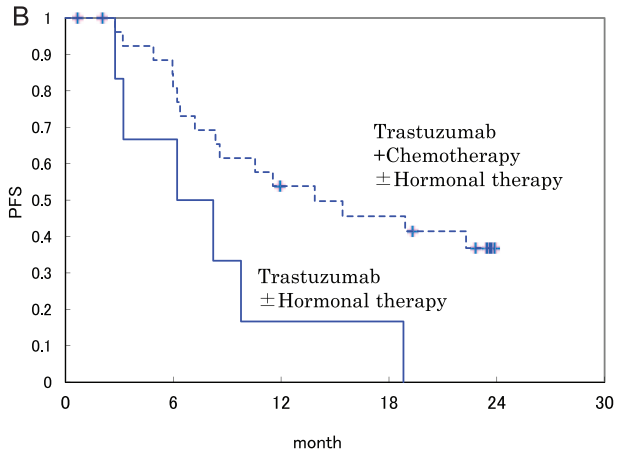
Overall survival

In all patients, the OS was analyzed using the Kaplan-Meier method. The 1- and 2-year cumulative survival rates and 95% CI were calculated. The 1- and 2-year survival rates were 93.9 (95% CI: 77.9%-98.4%) and 84.8% (95% CI: 67.4%-93.4%), respectively (Figure 2). The median survival rate and time were not reached.

Five patients died of breast cancer (primary disease). Among the five patients who died in this cohort, there were 2 cases of



Total		0y	1y	2y
All patients	No at risk	34	14	0
	PFS rate		46.9	29.8
	(95% CI)		(29.2-62.9)	(15.0-46.3)
PFS median (95% CI)		10.6 M	(6.4-18.9 M)	
PFS mean (95% CI)		13.7 M	(10.8-16.5 M)	



		0y	1y	2y
Trastuzumab+ Chemotherapy± Hormonal therapy	No at risk	28	13	0
	PFS rate		53.9	36.9
	(95%CI)		(33.4-70.7)	(18.7-55.2)
Trastuzumab ±Hormonal therapy	No at risk	6	1	0
	PFS rate		16.7	0.0
	(95%CI)		(0.8-51.7)	(0.0-0.0)

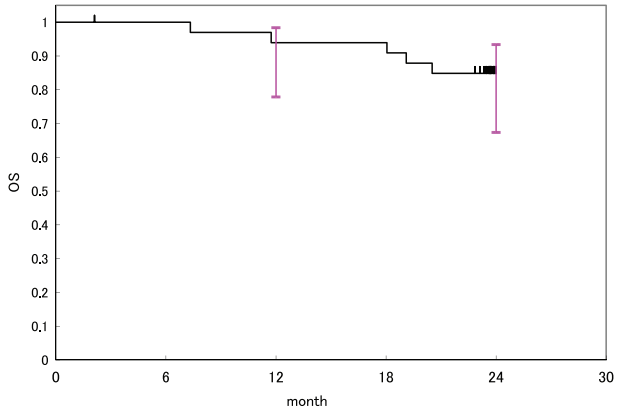
	median PFS(95%CI)	
Trastuzumab+Chemotherapy± Hormonal therapy	13.9	(7.2-NE)
Trastuzumab± Hormonal therapy	6.2	(2.8-NE)

(Continued)

Figure 1. (Continued)

Logrank test	p=0.020		
Cox regression analysis	Hazard raio	95% CI	p-valu
	2.993	(1.134-7.903)	0.027

Figure 1. (A) PFS in this cohort and (B) PFS stratified using chemotherapy. PFS indicates progression-free survival.



Total		0 y	1 y	2 y
All patients	No. at risk	34	32	4
	OS rate		93.9	84.8
	(95% CI)		(77.9 - 98.4)	(67.4 - 93.4)

Figure 2. OS in this cohort. CI indicates confidence interval; OS, overall survival.

PD, 2 cases of PR, and 1 case of best response SD. The 2 patients who died within 1 year after relapse had PD.

Safety

Adverse events were observed in 8 patients (23.5%): infusion reactions in 2, nausea in 1, and others in 5. There were no grade 3/4 adverse events. According to the NYHA (New York Heart Association) classification, 2 patients had grade I events. In all, 17 and 11 patients underwent ultrasonic cardiography 1 and 2 years after starting trastuzumab retreatment, respectively. One patient exhibited an absolute LVEF of 48%.

Discussion

Several randomized trials with trastuzumab have reported improved outcomes in patients with HER2-positive early breast cancer.[9–13] We here report the outcome of treatment of patients with HER2-positive early-stage breast cancer who received perioperative trastuzumab treatment. The 3-year relapse-free and OS rates were 94.2% and 98.9%, respectively.[14] Under these circumstances, it is becoming difficult to conduct clinical trials for patients with recurrent HER2-positive breast

cancer. Few data are available on patients who relapse after perioperative trastuzumab therapy.

Currently, as first-line therapy for HER2-positive recurrent breast cancer, combination therapy with pertuzumab, trastuzumab, and chemotherapeutic drugs is recommended according to the CLEOPATRA study.[4] In CLEOPATRA study, proportion of patients without a history of chemotherapy was 53%, and patients who had received trastuzumab accounted for only 10%. The median PFS was 18.5 months in the pertuzumab group and 12.4 months in the placebo (trastuzumab + docetaxel) group. However, in subgroups consisting of 88 patients who had been exposed to trastuzumab, the median PFS in pertuzumab and placebo group was 16.9 and 10.4 months, respectively. In our study, all patients had received adjuvant trastuzumab therapy and the median PFS for patients receiving trastuzumab combined with chemotherapy was 13.9 months. Although our results are inferior to the pertuzumab group, it seems to be better than placebo group (trastuzumab + taxans).

In EMILIA study,[5] patients with HER2-positive advanced or recurrent breast cancer, who had previously been treated with trastuzumab and taxans, were randomly assigned to T-DM1 or lapatinib plus capecitabine. The median PFS as assessed by independent review was 9.6 months with T-DM1 versus 6.4 months with lapatinib plus capecitabine. The objective response rate with T-DM1 was 43.6%. In HER2-positive recurrent breast cancer, the disease-free interval (DFI) was estimated as a predictive factor for the efficacy of trastuzumab retreatment,[15] however. In the CLEOPATRA and EMILIA study, the definitions of DFI differed from 12 months (CLEOPATRA) to 6 months (EMILIA), respectively, which may have influenced the results. In this study, DFI did not influence PFS.

In a phase 2 study involving patients similar to the subjects of this study, RHEA (Retreatment after HErceptin Adjuvant trial),[16] combination therapy with docetaxel or paclitaxel and trastuzumab was performed for 43 HER2-positive recurrent breast cancer patients who had received perioperative trastuzumab therapy for 10 months or more, as conducted in this cohort. The response rate was 61%. The median PFS was 8 months, and the median OS was 25 months. Our study may have included patients in whom not only taxans but also other chemotherapeutic regimens were combined with trastuzumab. In addition, distant metastases were present in all patients in the RHEA study, whereas visceral metastases were present in 16 patients (47%) in our study. Another observational study reported that the PFS of trastuzumab retreatment for patients who relapsed after perioperative trastuzumab treatment to be consistent for approximately 7 to 12 months.[15,17–19]

From our study, lack of chemotherapy with trastuzumab was identified as a poor prognostic factor.

Trastuzumab had reported synergistic with chemotherapy[3,10] and that monotherapy has quite limited activity. All patients with CR had received trastuzumab + chemotherapy ± hormone therapy in our study; chemotherapy should be used in combination with trastuzumab.

Concerning safety, we collected data on adverse events associated with trastuzumab or for which the association with trastuzumab could not be ruled out in this cohort. There were no grade 3/4 adverse events. No patient exhibited heart hypofunction requiring the discontinuation of trastuzumab administration. There is a possibility that the patients with cardiac function deterioration due to perioperative trastuzumab treatment was not registrated, and the fact that very few patients with hypertension in this cohort were affected, retreatment was safely performed in clinical practice.

Including our study, data on OS for anti-HER2 therapy for patients with HER2-positive metastatic/recurrent breast cancer are lacking. The optimal sequence for anti-HER2 therapy, including pertuzumab and T-DM1, needs to be set in the future. However, the number of patients with HER2-positive recurrent breast cancer may further decrease with advances in HER2-targeting perioperative treatment. The data from this study may aid in future research.

Conclusions

Although there are significant limitations of our study, in particular, the small sample size and short median follow-up, this study suggests that outcomes for trastuzumab retreatment in Japanese patients who relapsed after perioperative trastuzumab therapy were similar compared with those in previous reports. Differences in the patient background and treatments must be considered when interpreting the results. Trastuzumab should be used in combination with chemotherapy and/or hormonal therapy for retreatment. Retreatment with trastuzumab is safe.

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Author Contributions

HY contributed to concept development, study design, interpretation of the results, manuscript writing and funding for the project; MS, NM, YO, TT, ET, TS YS, KY, YK, TL, SO, KY, NY, KK, HS, SO and TI to conducting study, interpretation of the results and manuscript writing; SY to study design, data management, interpretation of the results and manuscript writing; SM to study design, interpretation of the results and statistical analyses; SO and MT to experimental design, interpretation of results and manuscript writing.

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