Efficacy of Adjuvant Combination Therapy With Trastuzumab and Chemotherapy in HER2-positive Early Breast Cancer: A Single Institutional Cohort Study from Clinical Practice

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Abstract. *Background/Aim:* To evaluate the improvement in the prognosis by adjuvant trastuzumab in clinical practice and the risk factors for distant recurrence, we retrospectively investigated the prognosis of HER2-positive early breast cancer in our department before and after the introduction of adjuvant trastuzumab. *Patients and Methods:* Cohorts A and B included 161 and 182 cases, respectively, who underwent surgery before (2000-2007) and after (2008-2015) the introduction of adjuvant trastuzumab. *Results:* The rates of relapse-free and distant metastasis-free survival were significantly better in cohort B than in cohort A. The risk factors of distant recurrence found in cohort A, such as the presence of lymph node metastasis, lymphatic invasion, and a low histological grade, did not increase the risk in cohort B. *Conclusion:* Many risk factors seemed to have been negated by adjuvant trastuzumab administration. Therefore, further escalation of adjuvant treatment should be carefully considered.

The overexpression of human epidermal growth factor-2 (HER2) occurs in approximately 15-20% of breast cancer patients and is associated with aggressive behavior of the tumor (1, 2). Several large randomized trials showed the prognostic benefits of the addition of trastuzumab (TZM) to standard adjuvant chemotherapy in patients with HER2-positive early breast cancer (EBC) (3-5). In Japan, 1-year adjuvant TZM for patients undergoing adjuvant

chemotherapy was approved for public insurance coverage in 2008 and since then has been widely used to treat HER2-positive EBC.

Most data showing the effect of adjuvant TZM have derived from phase 3 clinical trials, in which patients with lymph node positivity or with tumors larger than 10 mm were eligible (3, 4). However, because of the benefits, the indication of adjuvant TZM has been expanded to include patients with smaller tumors and node-negative patients (6). In our department, we usually proposed TZM plus chemotherapy to patients with HER2-positive EBC >10 mm in size, regardless of lymph node metastasis. In the case of tumors of 5-10 mm in size, we considered the use of TZM individually for each patient.

Adjuvant chemotherapy performed with or without TZM for HER2-positive EBC has also been improved. Cyclophosphamide, methotrexate, and fluorouracil (CMF) was the first adjuvant combination therapy for EBC (7, 8), but the effect of CMF was significantly inferior to anthracycline-containing chemotherapy for HER2-positive EBC (9). Because the addition of a taxane sequentially to an anthracycline-based regimen was shown to improve the outcome of high-risk EBC (10), anthracycline-based therapy followed by taxane became the standard chemotherapy combined with TZM (3, 4).

The combination of pertuzumab, TZM and docetaxel has been shown to have a significant survival benefit in patients with HER2-positive metastatic breast cancer (11, 12). A similar benefit of pertuzumab was expected in the adjuvant setting and pertuzumab significantly improved the rates of invasive-disease-free survival among patients with HER2-positive EBC (13). However, the addition of pertuzumab had only a small effect in the node-negative population and was associated with toxic effects, such as mild diarrhea. The combination of TZM and chemotherapy might be sufficient in low-risk patients.

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Table I. Clinicopathological backgrounds of the patients in cohort A and cohort B.

Characteristics	Cohort A (n=161)		Cohort B (n=182)		p-Value
	No.	%	No.	%	
Age mean (SD)	54.4 (9.2)		56.4 (10.3)		0.059
Pathological tumor stage					
-T1b	30	18.6%	40	22.0%	0.50
T1c-	130	80.7%	142	78.0%	
Missing	1	0.6%	0	0.0%	
Pathological nodal stage					
N (-)	100	62.1%	126	69.2%	0.17
N (+)	61	37.9%	56	30.8%	
Histological grade (HG)					
HG1, 2	69	42.9%	76	41.8%	0.660
HG3	87	54.0%	106	58.2%	
Missing	5	3.1%	0	0.0%	
ly factor					
ly (-)	104	64.6%	139	76.4%	0.018
ly (+)	57	35.4%	43	23.6%	
v factor					
v (-)	145	90.1%	175	96.2%	0.030
v (+)	16	9.9%	7	3.8%	
Hormone receptor status					
Negative	89	55.3%	60	33.0%	<0.001
Positive	72	44.7%	122	67.0%	
ER (+), PgR (+)	41	25.5%	87	47.8%	0.016**
ER (+), PgR (-)	26	16.1%	34	18.7%	
ER (-), PgR (+)	5	3.1%	1	0.5%	
Adjuvant endocrine therapy					
No	95	59.0%	75	41.2%	0.001*
Yes	66	41.0%	107	58.8%	
SERM	37	23.0%	42	23.1%	0.18**
AI	39	24.2%	67	36.8%	
Adjuvant chemotherapy					
No	48	29.8%	32	17.6%	0.02*
Yes	113	70.2%	150	82.4%	
CMF	15	9.3%	0	0.0%	<0.001**
Anthracycline-based	51	31.7%	30	16.5%	
Taxane-based	3	1.9%	9	4.9%	
Anthracycline and Taxane	43	26.7%	110	60.4%	
Others	1	0.6%	1	0.5%	
Adjuvant trastuzumab					
No	148	91.9%	38	20.9%	<0.001
Yes	13	8.1%	144	79.1%	

SERM: Selective estrogen receptor modifier; CMF: cyclophosphamide, methotrexate, and fluorouracil. *Fisher's exact test between "Yes" and "No"; **Fisher's exact test among sub-category.

In this study, we examined the benefit of TZM therapy in real-world practice by comparing the survival rates of HER2-positive EBC patients between two different periods; before and after the approval of adjuvant TZM. Moreover, we investigated the risk factors for recurrence in each period in order to determine the subgroup in which the efficacy of TZM-containing chemotherapy would be insufficient and in which more intensive treatment, such as pertuzumab, would be necessary.

Patients and Methods

Patient population. We identified all pathological stage I-III EBC patients who underwent surgery without neoadjuvant systemic therapy for primary breast cancer in the Department of Breast Oncology, National Hospital Organization Kyushu Cancer Center between 2000 and 2015. Among them, patients aged ≤ 75 years with HER2-positive EBC were included in this study. The clinical data were obtained from the patients' medical records. The AJCC/UICC TNM classification and stage groupings were used. Written

Table II. Adjuvant systemic treatments in each cohort.

Cohort A (n=161)										Cohort B (n=182)											
		CT (-)		CT (+)		<i>p</i> -Value*		CT (+)				CT (-)		CT (+)		<i>p</i> -Value*		CT (+)		<i>p</i> -Value**	

CT: Chemotherapy; TZM: trastuzumab; HG: histological grade; HR: hormone receptor. *Fisher's exact test comparing between factors; **Fisher's exact test comparing between cohorts (Cohort A vs. Cohort B).

informed consent was obtained from all patients before collecting tissue samples. This study was approved by the institutional review board of our hospital.

The expression of estrogen receptor (ER) and progesterone receptor (PgR) were regarded as positive if their nuclear expression was $\geq 1\%$ and hormone receptor (HR) was regarded as positive in cases that were either ER-positive or PgR-positive. The HER2 status was evaluated according to the recommendations of ASCO/CAP (14).

Patients were divided into two groups, cohort A and cohort B, according to the year of surgery. Patients in cohort A underwent breast cancer surgery from 2000 to 2007 (when TZM was not used in the adjuvant setting outside clinical trials). Patients in cohort B underwent breast cancer surgery from 2008 to 2015 (when it became possible to use TZM in the adjuvant setting).

Statistical analyses. The statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for the R software program (The R Foundation for Statistical Computing, Vienna, Austria) (15). The average of age was compared between the cohorts using a *t*-test. Fisher's exact tests were used to compare the proportions of categorical variables. Relapse-free survival (RFS) was defined as the time from surgery to the first breast cancer event, including loco-regional recurrence, distant metastasis, or the development of a new cancer in the contralateral breast. Distant metastasis-free survival (DMFS) was defined as the time from surgery until the development of distant metastasis. Overall survival (OS) was defined as the time from surgery to death from any cause. Survival was estimated using the Kaplan–Meier method and the estimated survival in each clinicopathological subgroup was compared using the log-rank test. *p*-Values of <0.05 were considered to indicate statistical significance. A Cox proportional hazards model was used to perform univariate and multivariate analyses of risk factors. Baseline variables with $p<0.05$ in univariate analysis were included in the multivariable models.

Results

Patient characteristics. We identified 343 patients of 75 years of age or younger who were diagnosed with pathological stage I-III HER2-positive EBC and who underwent surgery without neoadjuvant treatment in our department between 2000 and 2015. Table I shows the clinicopathological characteristics of the study population in cohorts A (n=161) and B (n=182). Patients in cohort A showed more frequently lymphovascular invasion. Patients in cohort B showed more frequently HR positivity, and more frequently received adjuvant endocrine therapy. In cohort A, 71.4% of patients received postoperative chemotherapy, but only 8.1% of the patients received TZM-containing therapy. In group B, 79.1% of patients received TZM-containing postoperative chemotherapy. In addition to the percentage of patients who received chemotherapy, the contents of adjuvant chemotherapy differed between the two cohorts. In the cohort A, anthracycline and taxane-based chemotherapy was administered only in 26.7% of the patients, but in the cohort B, anthracycline and taxane-based chemotherapy was administered in 60.4% of the patients. The CMF regimen was not chosen in cohort B. Low histological grade (HG) was significantly associated with HR positivity in both cohorts ($p<0.001$, data not shown).

In cohort A, postoperative chemotherapy (including a small number of patients who received combination therapy with TZM) was more often used for patients with a large tumor size, lymph node metastasis, and HR negativity (Table II). In cohort B, except for patients with a small (-T1b) tumor size, TZM-containing chemotherapy was used. The

Figure 1. Kaplan-Meier plots in each cohort for relapse-free survival (A), distant metastasis-free survival (B), and overall survival (C). *p*-Values were determined by a log-rank test. Five-year survival rates are shown.

HR expression did not influence the application of chemotherapy in cohort B. Chemotherapy without TZM was selected in exceptional cases in cohort B. The comparison of cohort B with cohort A showed that the introduction of

chemotherapy (with or without TZM) was significantly increased in the subgroups of patients with large-size tumors, patients without lymph node metastasis, patients with high HG and patients with HR positivity (Table II).

Table III. Risk factors for distant metastasis in cohort A.

Factors		Univariate analysis			Multivariate analysis		
		Hazard ratio	95%CI	p-Value	Hazard ratio	95%CI	p-Value
pT stage	T1c- vs. -T1b	3.480	0.827-14.64	0.09			
pN stage	N (+) vs. N (-)	6.226	2.668-14.53	<0.001	3.668	1.368-9.831	0.010
	N2-3 vs. N0-1	2.376	1.005-5.353	0.037			
	N3 vs. N0-2	2.833	0.984-8.158	0.057			
Histological grade (HG)	HG3 vs. HG1,2	0.447	0.212-0.943	0.034	0.412	0.190-0.892	0.024
ly	ly (+) vs. ly (-)	3.826	1.817-8.057	<0.001	2.310	0.972-5.505	0.06
v	v (+) vs. v (-)	3.272	1.391-7.694	0.007	1.967	0.817-4.739	0.1
Hormone receptor (HR)	HR (+) vs. HR (-)	1.898	0.914-3.942	0.09			
Adjuvant chemotherapy	Yes vs. No	1.715	0.699-4.208	0.2			

Table IV. Risk factors for distant metastasis in cohort B.

Factors		Univariate analysis			Multivariate analysis		
		Hazard ratio	95%CI	p-Value	Hazard ratio	95%CI	p-Value
pT stage	T1c- vs. -T1b	2.198	0.279-17.35	0.455			
pN stage	N (+) vs. N (-)	1.360	0.384-4.820	0.634			
	N2-3 vs. N0-1	3.376	0.873-13.06	0.078			
	N3 vs. N0-2	4.975	1.056-23.44	0.042			
Histological grade (HG)	HG3 vs. HG1,2	2.437	0.517-11.48	0.260			
ly	ly (+) vs. ly (-)	0.794	0.168-3.740	0.770			
v	v (+) vs. v (-)	9.511	1.994-45.38	0.005			
Hormone receptor (HR)	HR (+) vs. HR (-)	0.815	0.230-2.888	0.751			
Adjuvant chemotherapy	Yes vs. No	0.370	0.096-1.431	0.150			

Relapse-free survival, distant-metastasis free survival, and overall survival. The estimated 5-year RFS rates in cohorts A and B were 80.2% and 92.5%, respectively (Figure 1A). The 5-year DMFS rates in cohorts A and B were 85.9% and 93.1%, respectively (Figure 1B). The 5-year OS rates in cohorts A and B were 95.0% and 95.8%, respectively (Figure 1C). RFS and the DMFS were significantly improved in cohort B in comparison to cohort A in log-rank tests ($p=0.002$ and $p=0.016$, respectively).

Risk factors for distant metastasis in each period. A univariate analysis indicated that pathological lymph node involvement, low HG, lymphatic invasion and vascular invasion were significantly associated with recurrence with distant metastasis in cohort A (Table III). The HR status was not significantly associated with DMFS; however, the Kaplan–Meier curve of DMFS for the HR-positive group continued to decline over 5 years (Figure 2C). A multivariate analysis identified lymph node involvement and low HG as independent risk factors for distant metastasis in cohort A. However, vascular invasion was the only risk factor for distant metastasis in cohort B in the

univariate and multivariate analyses. In cohort B, we examined whether more extensive lymph node metastasis would worsen DMFS. By comparing patients with pathological stage N2-3 to those with N0-1 or patients with pathological stage N3 to those with N0-2, we found that the hazard ratio gradually increased to 3.376 (0.873-13.06, $p=0.078$) and to 4.975 (1.056-23.44, $p=0.042$) (Table IV). The Kaplan–Meier curves of DMFS classified by each risk factor in each periodical cohort are shown in Figure 2.

Discussion

In this study, we investigated the impact of adjuvant TZM together with improved chemotherapy on the outcomes of HER2-positive EBC in our department by comparing the period before the advent of adjuvant TZM to the period after the advent of adjuvant TZM. We found that overall survival did not significantly improve, but the recurrence rate significantly decreased in the latter period. The benefit of adjuvant TZM with appropriate chemotherapy in HER2-positive EBC was confirmed in real world data from a single institution.

Figure 2. Kaplan-Meier plots for distant metastasis-free survival for cohort A (A-E) and cohort B (F-J). Plots were drawn for subgroups classified by the pathological lymph node status (A, F), histological grade (B, G), hormone receptor status (C, H) lymphatic invasion (D, I), and vascular invasion (E, J).

Previous studies have shown that many factors, including young age, large tumor size, lymph node metastasis, lymphovascular invasion and high HG increase the risk of recurrence after primary treatment of EBC (16, 17). In the present study, the results of the univariate analyses showed that the presence of lymph node metastasis, low HG and the presence of lymphatic involvement were risk factors for distant metastasis in the early period. Low HG might be related to resistance to cytotoxic chemotherapy (18, 19). However, in the latter period, these factors did not significantly worsen DMFS. Vascular involvement was the only risk factor for metastatic recurrence in both periods.

In HER2-positive EBC, the absence of HR expression has been reported to be a risk factor for recurrence (20). In our study, HR negativity was likely to be a preferable factor of distant recurrence after over 5 years but not significantly, in cohort A.

Recently, new anti-HER2 agents have been developed and escalated adjuvant treatment strategies were considered. In the ExteNET study, the efficacy and safety of 12 months of neratinib, a tyrosine-kinase inhibitor of HER1, HER2, and HER4, after TZM-based adjuvant therapy were investigated in patients with HER2-positive EBC (21, 22). Neratinib could significantly improve 2-year invasive disease-free survival, but some adverse effects, such as diarrhea were observed. In the APHINITY trial, the combination of pertuzumab, TZM and standard chemotherapy could reduce the recurrence of HER2-positive EBC (13). The effect of pertuzumab in low-risk groups, such as node-negative EBC, was very small and chemotherapy combined with TZM alone might be sufficient in this population. In our study, lymph node metastasis was an independent risk factor for recurrence in cohort A. In cohort B, lymph node metastasis was not a risk factor for recurrence; however, the relative risk of distant metastasis gradually increased in association with the pathological lymph node stage. The use of TZM with appropriate chemotherapy has been eliminating the gap in the risk of recurrence due to lymph node metastasis; however, there is probably room to consider more potent treatment in cases with extensive lymph node involvement.

In contrast, studies of de-escalation in adjuvant therapy for HER2-positive EBC have been reported (6, 23-26). In the APT trial, 1-year TZM combined with only 12-week paclitaxel was administered for patients with HER2-positive EBC of up to 3 cm without lymph node metastasis (6). The result was satisfactory, and this regimen was thought to be an option for stage I disease. All trials evaluating the non-inferiority of short duration (6 months or 12 weeks) TZM in comparison to 1-year TZM, except for the PERSEPONE study, could not prove non-inferiority; however, there were small differences in survival benefits. However, the possibility of cardiac adverse events apparently decreased in de-escalation groups. We did not choose pre-planned shorter

TZM treatments; however, cases in which TZM cannot be completed due to adverse effects, the discontinuation of TZM might be acceptable.

The present study was associated with some limitations, including its retrospective design. The comparison between two cohorts could be influenced by differences in patient background factors and the changes in the medical environment. However, we intended to show the extent to which the introduction of adjuvant TZM with appropriate chemotherapy could improve the prognosis of high-risk patients in comparison to low-risk patients in clinical practice.

In conclusion, adjuvant TZM could reduce recurrence in HER2-positive EBC patients in a real-world clinical setting and prognostic differences between the high-risk group and the low-risk groups were almost eliminated. We can choose an escalation strategy for high-risk patients, such as those with extensive lymph node metastasis, but with careful consideration of the possible benefits, additional adverse effects and expenses.

Conflicts of Interest

The Authors have no conflicts of interest regarding the present study.

Authors' Contributions

M.O., W.T., H.U., T.M., H.I., C.K., Y.N. and K.T. analyzed the data and assisted with data interpretation; M.O. and E.T. conceived the study; M.O. drafted the manuscript; M.O., S.O., and E.T. contributed to discuss and review the final manuscript; all Authors approved the final manuscript.

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