tumor who were treated with NAC with trastuzumab. They reported that pCR, clinical tumor stage, and lymphovascular invasion were independent predictors for DFS. In our study, pCR and spCR were predictors for DFS; in addition, conventional prognostic factors such as nodal stage and histological/nuclear grade were predictors for DFS.

In this study, the association of age with DFS was not statistically significant in the whole dataset, consistent with the results of the TECHNO trial and Kim et al. Partridge et al. [17] reported that young age was not associated with worse DFS in patients with HER2-positive disease using large cohort data from the HERA trial. When we divided the patients into ER/PgR-positive and -negative groups, multivariate analysis showed that young age (age $\leq$40) was an independent predictor for poorer DFS in the ER/PgR-positive dataset. Our result was consistent with earlier studies showing that younger age is an independent predictor for worse DFS, especially in patients with ER/PgR-positive disease [18, 19].

After dividing the patients into ER/PgR-positive and -negative datasets, we performed multivariate analysis for DFS using each dataset. About 30–40 % of HER2-enriched subtype tumors are reported to be ER positive [20, 21]. Among clinically HER2-positive tumors, up to 60 % are classified as the HER2-enriched subtype, with the rest classified as luminal B, luminal A, or basal-like [22]. Adjuvant systemic therapy differs according to ER/PgR status [23]. Therefore, it seemed reasonable to perform the analysis based on ER/PgR status; however, the results should be interpreted carefully because of the relatively small event rate in each dataset.

In relation to the two aforementioned meta-analyses, pooled analysis from the German study group [6] indicated that pCR was a prognostic factor for the HER2-positive non-luminal subgroup, but not for those in the HER2-positive luminal subgroup. In the meta-analysis from the Collaborative Trials in Neoadjuvant Breast Cancer (CTNeoBC) [16], there was a stronger association of pCR with event-free survival in the HER2-positive non-luminal subgroup compared with those in the HER2-positive luminal subgroup. In our study, pCR was an independent predictor for DFS in the ER/PgR-negative dataset, but not ER/PgR-positive dataset, and spCR was an independent predictor for DFS regardless of ER/PgR status.

The limitations of this study include its retrospective design. Adjustment using multivariate analysis is mandatory to minimize selection bias. The relatively short observation period may also limit the interpretation of our results. The median follow-up period of our study (42 months) covered the time when recurrence risk is high in HER2-positive disease [24]. Strength of our study was the large number of patients, which allowed us to conduct multivariate analysis separately according to ER/PgR status.

In conclusion, pCR/spCR, nodal status, and grade were predictors for DFS in patients with HER2-positive disease treated with NAC plus trastuzumab. Response to therapy and prognostic impact of the factors differed according to ER/PgR status. Our results may help identify patients who are not likely to achieve pCR or whose outcome would otherwise be unfavorable. New treatment approaches, such as the incorporation of novel anti-HER2 drugs, are needed for patients with high-risk disease.

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EPIDEMIOLOGY

Prognostic factors of HER2-positive breast cancer patients who develop brain metastasis: a multicenter retrospective analysis

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Abstract The clinical course and prognostic factors of HER2-positive breast cancer patients with brain metastases are not well known because of the relatively small population. The aim of this study was to determine prognostic factors associated with HER2-positive patients who develop brain metastases. This retrospective study assessed the largest dataset to date of 432 HER2-positive patients who were diagnosed with brain metastases from 24 institutions of the Japan Clinical Oncology Group, Breast Cancer Study Group. The median age of the 432 patients was 54 years (range, 20–86 years). Of the patients, 162 patients (37.5 %) had ER-positive/HER2-positive (ER+HER2+) breast cancer, and 270 (62.5 %) had ER-negative/HER2-positive (ER−HER2+) breast cancer. The median brain metastasis-free survival period from primary breast cancer was 33.5 months in both groups. The median survival after developing brain metastasis was 16.5 and 11.5 months in the ER+HER2+ and ER−HER2+ groups, respectively, ($p = 0.117$). Patients with >3 brain metastases had significantly shorter overall survival in both ER+HER2+ ($p < 0.001$) and ER−HER2+ ($p = 0.018$) groups. Treatment with trastuzumab before developing brain metastases was not associated with survival duration after developing brain metastases ($p = 0.571$). However, patients treated with both trastuzumab and lapatinib after developing metastasis had significantly longer survival than patients treated with trastuzumab alone, lapatinib alone, or no HER2-targeting agent ($p < 0.001$). For HER2-positive patients with brain metastases, regardless of the use of trastuzumab before developing brain metastasis, treatment with both trastuzumab and lapatinib might improve survival.

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Introduction

Human epidermal growth factor receptor 2 (HER2) is overexpressed and/or amplified in approximately 15–25 % of breast cancers [1, 2]. Compared to chemotherapy alone, the addition of trastuzumab, a monoclonal HER2-targeting antibody, to chemotherapy prolongs progression-free survival and overall survival (OS) in patients with metastatic disease [3, 4]. However, patients with HER2-positive breast cancer have a high risk of developing brain metastasis compared to other subtypes of breast cancer. In a retrospective analysis using the largest dataset to date of 1,256 patients with brain metastasis, we recently reported that the prognosis and clinical course of patients with brain metastasis from breast cancer before and after developing the metastases vary according to subtype [5]. While surgery and irradiation therapy should be considered the first approach for local control of brain metastasis, a standard systemic treatment including the HER2-targeting agents for brain metastasis has not been established. In addition, the clinical course and prognostic factors of HER2-positive breast cancer patients with brain metastases are not well known because of the relatively small population of these patients. The aim of this study, therefore, was to determine the clinicopathologic factors associated with the prognosis of patients with positive HER2 who develop brain metastasis.

Methods

Patients

This study was planned under the auspices of the Japan Clinical Oncology Group, Breast Cancer Study Group, which includes 34 clinical institutions in Japan. The eligibility criteria for this study were described in our previous study [5]. We retrospectively identified patients diagnosed with brain metastasis as the first recurrence of breast cancer during follow-up and those who developed brain metastases during systemic treatment for metastatic disease. The presence of brain metastases was defined on the basis of magnetic resonance imaging and/or CT scans. A large dataset of 432 HER2-positive breast cancer patients who were diagnosed with brain metastases between April 1, 2001 and December 31, 2012 was collected from 24 institutions. This study was approved by the institutional review board of each participating institute. The need for written informed consent was waived because of the retrospective nature of the study.

Pathologic assessment

The primary tumors were histologically classified using the World Health Organization criteria [6]. Histological grading was assessed using the Nottingham grading system [7]. HER2 positivity was defined as a receptor overexpression staining score of 3+ on immunohistochemical analysis or by gene amplification with fluorescence in situ hybridization [8]. Samples from the primary tumors were considered hormone receptor positive if $\geq$10 % of the cells had nuclear staining for ER or progesterone receptor on immunohistochemical analysis.

Statistical methods

We assessed OS for patients with brain metastases according to ER status, histological grade, presence of symptoms at the time of diagnosis of brain metastasis, number of brain metastases, and treatment with HER2-targeting agents. The definition of survival duration was the same as the definition described in our previous study [5]. Brain metastasis-free survival (BMFS) was defined as the

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time interval from the diagnosis of primary breast cancer until the diagnosis of brain metastasis or the last follow-up date. Overall survival was defined as the length of time from the diagnosis of brain metastases to death or to the last follow-up date. BMFS and OS were estimated using the Kaplan–Meier method. Cox proportional hazards models were used to determine the association between prognosis and clinicopathologic factors. All statistical analyses were done using SPSS software, version 21 (SPSS Inc., Chicago, IL, USA); p values less than 0.05 were considered statistically significant.

Results

Clinical characteristics

Clinicopathologic characteristics of the 432 HER2-positive patients who were diagnosed with brain metastases from breast cancer are summarized in Table 1. The median age of the 432 patients was 54 years (range, 20–86 years), and the median follow-up time was 50.6 months. Of the patients, 162 patients (37.5 %) had ER-positive/HER2-positive (ER+HER2+) primary breast cancer, and 270 patients (62.5 %) had ER-negative/HER2-positive (ER−HER2+) breast cancer. The median BMFS period from the time of diagnosis of primary breast cancer was 33.5 month in both groups. For 63.4 % of patients with ER+HER2+ breast cancer and 75.6 % of patients with ER−HER2+ breast cancer, brain metastases were detected within 2 years after development of the first distant metastasis. Eighty-four patients with ER+HER2+ breast cancer (52 %) and 133 patients with ER−HER2+ breast cancer (49 %) had more than three brain metastases at the time of diagnosis.

One hundred thirteen patients with ER+HER2+ (70 %) and 187 patients with ER−HER2+ (69 %) were treated with trastuzumab before the diagnosis of brain metastasis. After the diagnosis of brain metastasis, 108 patients with ER+HER2+ (63 %) and 175 patients with ER−HER2+ (64 %) were treated with HER2-targeting agents, including trastuzumab and/or lapatinib. Nineteen of the 162 patients with ER+HER2+ (12 %) and 53 of the 270 patients with ER−HER2+ (20 %) underwent surgery for the brain metastases.

Table 1 Patients characteristics

	Total (n = 432)		ER+HER2+ (n = 162)		ER−HER2+ (n = 270)	
ER						
Positive	162	37.5 %	162	100.0 %	0	0.0 %
Negative	270	62.5 %	0	0.0 %	270	100 %
Symptoms						
Symptomatic	325	75.2 %	121	74.7 %	204	75.6 %
Asymptomatic	89	20.6 %	36	22.2 %	53	19.6 %
Unknown	18	4.2 %	5	3.1 %	13	4.8 %
Number of brain metastases						
3 or less	190	44.0 %	72	44.4 %	118	43.7 %
More than 3	217	50.2 %	84	51.9 %	133	49.3 %
Unknown	25	5.8 %	6	3.7 %	19	7.0 %
Treatment for brain metastases						
Operation	72	16.7 %	19	11.7 %	53	19.6 %
STI	118	27.3 %	52	32.1 %	66	24.4 %
WBI	206	47.7 %	74	45.7 %	132	48.9 %
No treatment	5	1.2 %	3	1.9 %	2	0.7 %
Unknown	31	7.2 %	14	8.6 %	17	6.3 %
Time from relapse to development of brain metastases						
Less than 6 months	130	30.1 %	45	27.8 %	85	31.5 %
More than 6 months	275	63.7 %	105	64.8 %	170	63.0 %
Unknown	27	6.2 %	12	7.4 %	15	5.6 %
Histological grade						
G1	29	6.7 %	15	9.3 %	14	5.2 %
G2	81	18.8 %	40	24.7 %	41	15.2 %
G3	137	31.7 %	34	21.0 %	103	38.1 %
Unknown	185	42.8 %	73	45.1 %	112	41.5 %

Revised from Niikura et al. [5]

STI stereotactic radiotherapy, *WBI* whole brain radiotherapy

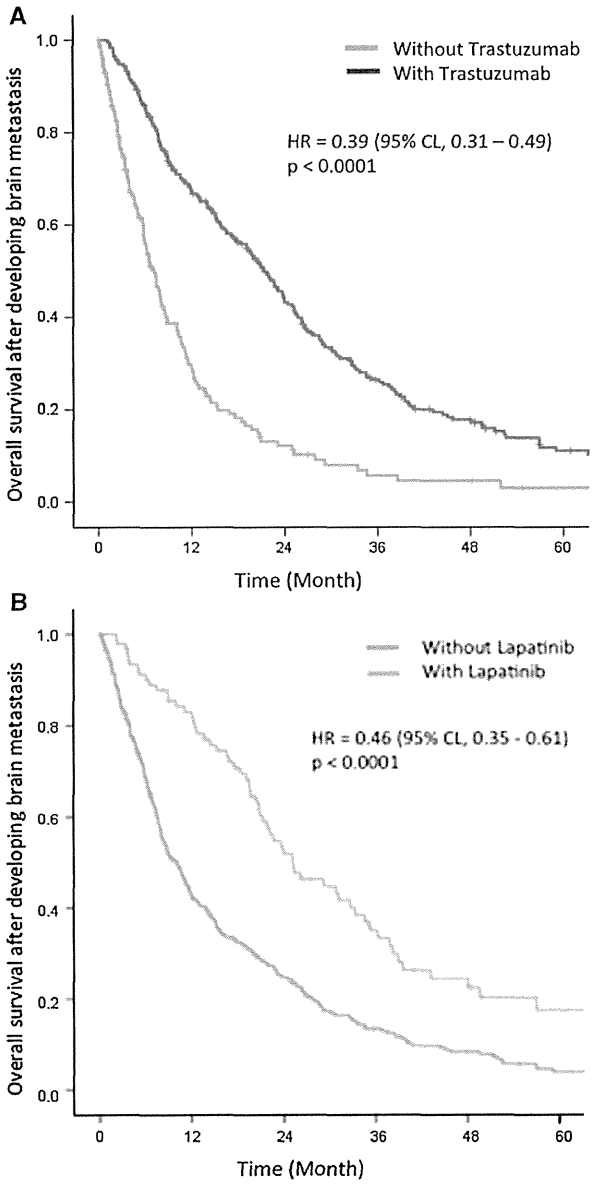

Fig. 1 Overall survival after developing brain metastases in HER2-positive breast cancer patients according to **a** treatment with/without trastuzumab ($p < 0.001$), and **b** treatment with/without lapatinib ($p < 0.001$). *HR* hazard ratio, *CI* confidence interval

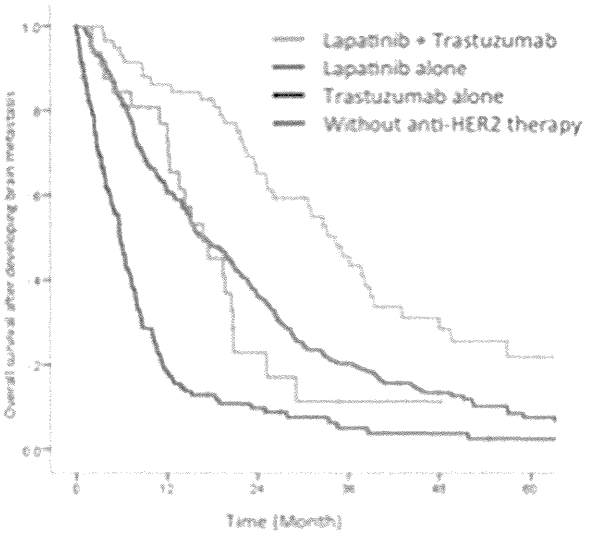

Fig. 2 Overall survival after developing brain metastases according to anti-HER2 agents in HER2-positive breast cancer patients ($p < 0.001$)

Treatment outcomes

The median survival after developing brain metastasis was 16.5 months (95 % confidence interval [CI] 11.9–21.1 months) for patients with ER+HER2+ and 11.5 months (95 % CI 9.1–13.8 months) for patients with ER−HER2+ ($p = 0.117$). Patients with more than three brain metastases had a significantly shorter OS than patients with three or fewer brain metastases in both the ER+HER2+ group ($p < 0.001$) and the ER−HER2+ group ($p = 0.018$).

Patients treated with trastuzumab (Fig. 1a) or lapatinib (Fig. 1b) after developing brain metastasis had significantly longer survival than patients who did not receive these agents ($p < 0.001$). Furthermore, patients treated with both trastuzumab and lapatinib had a significantly longer survival than patients who were treated with trastuzumab alone, lapatinib alone, or no HER2-targeting agent ($p < 0.001$) (Fig. 2).

Univariate and multivariate analysis of prognostic factors

We assessed the prognostic impact of HER2-targeting agents and other clinicopathologic factors for the 432 patients with brain metastasis (Table 2). In univariate analysis of the clinicopathologic factors, we found that the presence of ≤3 brain metastases (hazard ratio [HR] 0.62; 95 % CI 0.49–0.77; $p < 0.001$), treatment with trastuzumab after the diagnosis of brain metastases (HR 0.39; 95 % CI 0.31–0.49; $p < 0.001$), and treatment with lapatinib after the diagnosis of brain metastases (HR 0.46; 95 % CI 0.35–0.61; $p < 0.001$) were associated with a decreased risk of death during the follow-up period. Treatment with trastuzumab before developing brain metastases was not associated with the duration of survival after developing brain metastases ($p = 0.571$). In multivariate analysis, these three factors were the sole independent favorable prognostic factors of OS (three or fewer brain metastases, $p = 0.006$; trastuzumab, $p < 0.001$; and lapatinib, $p < 0.001$).

Table 2 Univariate and multivariate analysis of factors associated with survival after developing brain metastasis

	Univariate analysis				Multivariate analysis			
	HR	95.0 % CI		*p*	HR	95.0 % CI		*p*
Symptom of brain metastases (symptomatic/asymptomatic)	1.047	0.80	1.35	0.727				
Number of brain metastases (3 or less/more than 3)	0.62	0.49	0.77	<0.0001	0.725	0.576	0.912	0.006
ER (positive/negative)	0.83	0.67	1.04	0.117				
Trastuzumab before developing brain metastases	1.074	0.84	1.374	0.571				
Trastuzumab after developing brain metastases	0.39	0.31	0.49	<0.0001	0.445	0.352	0.563	<0.0001
Lapatinib after developing brain metastases	0.46	0.35	0.61	<0.0001	0.510	0.383	0.679	<0.0001
Histological grade (G1 and G2/G3)	1.065	0.804	1.412	0.659				

HR hazard ratio, *CI* confidence interval

Discussion

Our results from the largest study to date that analyzed the clinical data of HER2-positive breast cancer patients with brain metastases clearly showed that patients who were treated with both trastuzumab and lapatinib after developing brain metastases had significantly longer survival than patients who were treated with trastuzumab alone, lapatinib alone, or no HER2-targeting agent. Another novel finding of this study was that the use of trastuzumab before developing brain metastases did not affect the duration of survival after developing brain metastases. Therefore, we suggest treatment with both of these HER2-targeting agents to control brain metastasis in addition to current standard therapies, including surgery and irradiation therapy. Finally, we showed that HER2-positive patients with more than three brain metastases at the diagnosis had a poor prognosis regardless of ER positivity, but treatment with both HER2-targeting agents might improve their survival.

Since the approval by the U.S. Food and Drug Administration of the use of trastuzumab for metastatic HER-2 positive breast cancer in 1998 and as an adjuvant therapy in 2006, the survival of patients with HER2-positive breast cancer has been dramatically prolonged. In addition, we have previously shown that for patients with ER+HER2+ primary breast cancer, hormonal therapy confers a survival benefit when added to chemotherapy and trastuzumab [9]. Despite the improvement in survival, however, overexpression of HER2 is an independent factor for the development of brain metastasis [10, 11]. Brufsky et al. reported CNS metastases in 377 (37.3 %) of 1,012 patients with confirmed HER2-positive tumors [3]. While HER2 status has been shown to be associated with the risk of brain metastases, the association between the use of trastuzumab and brain metastases is less clear. One meta-analysis revealed that the use of trastuzumab in the adjuvant setting was significantly associated with an increased risk of the central nervous system (CNS), being the first site of recurrence in HER2-positive breast cancer patients [12], whereas the HERA trial did not show an increased risk of CNS metastasis [13].

We recently reported that patients with different subtypes of breast cancer with brain metastases showed different prognoses and time to development of brain metastases. Regardless of ER positivity, HER2 status was found to be a good prognostic factor for survival after the diagnosis of brain metastasis [9]. Interestingly, the use of trastuzumab in the adjuvant setting or metastatic setting prior to the development of brain metastasis did not affected prognosis once patients had developed brain metastasis.

It has been thought that trastuzumab is unable to penetrate the blood–brain barrier (BBB) and can better control extracranial metastases, which would lead to an increased risk of brain metastases in patients with HER2-positive breast cancer and a decreased risk of extracranial distant metastases [12, 14–16]. However, Tamura analyzed the PET scan images of patients with HER2-positive breast cancer who were given 64Cu-DOTA-trastuzumab and determined that the compound reached brain metastases through the BBB [17]. This finding supported our results that the use of trastuzumab improved survival in patients who were treated with trastuzumab after developing brain metastasis, even though it was not adequately effective for complete remission of the brain metastasis.

Lapatinib, a dual HER1/HER2 tyrosine kinase inhibitor, is another commercially available HER2-targeting agent. The use of lapatinib in combination with capecitabine as a second-line treatment for patients with HER2-positive metastatic breast cancer previously treated with trastuzumab has been shown to prolong the time to progression compared to capecitabine alone [18, 19]. In these phase three randomized studies, the benefit in time to progression

has been shown 12.7 weeks (31.3 vs 12.6 weeks) and 4 months (8.4 vs 4.4 months).Furthermore, the response rate of CNS metastases, defined as at least more than 20 % of volumetric reduction in MRI or CT scan findings, to this combination therapy has been found to be up to approximately 40 % (21–50 %) [20–24]. For patients with previously untreated HER2-positive breast cancer and brain metastases, the combination of lapatinib and capecitabine was associated with an objective CNS response in 29 of 48 patients (65.9 %), and this combination therapy yielded a 5.5-month median time to progression and a 17-month median OS time (range, 13.7–24.9 months) [25]. However, 49 % of treated patients had grade 3 or grade 4 treatment-related adverse events, including diarrhea and hand–foot syndrome. Lapatinib is a small molecule agent and can theoretically penetrate the BBB. However, the CEREBEL trial recently showed no advantage of lapatinib with capecitabine compared to trastuzumab with capecitabine in the development of CNS metastases, because of the small number of CNS events [26]. In our study, patients who were treated with both trastuzumab and lapatinib after developing brain metastases had a significantly longer survival period compared to those who received either a single or no HER2-targeting agent. A similar effect was demonstrated in a retrospective analysis of patients with brain metastasis who had previously received lapatinib or trastuzumab. Patients treated with a combination of these anti-HER2 agents had a longest OS than those treated with lapatinib alone, trastuzumab alone, and no anti-HER2 agent (25.9, 21.4, 10.5, and 5.7 months, respectively, $p < 0.001$) [27]. Further evaluation of the mechanism of lapatinib against brain metastasis is needed.

Other novel HER2-targeting agents, including pertuzumab and T-DM1, have been found to be effective against brain metastases. Pertuzumab is a HER2-targeting agent that works as a HER-dimerization inhibitor. The CLEOPATRA, a randomized double-blind placebo-controlled phase III trial, demonstrated that a combination use with pertuzumab, trastuzumab and docetaxel improved PFS and OS even for HER2-positive metastatic breast cancer patients with CNS metastases [28]. In that study, the incidence of CNS metastases as the first site of disease progression was similar in the placebo arm (12.6 %) and the pertuzumab arm (13.7 %). However, the addition of pertuzumab to trastuzumab therapy delayed the onset of CNS disease [28]. Trastuzumab emtansine (T-DM1) is a novel antibody-cytotoxin conjugate that was recently approved for use in the treatment of patients with metastatic HER2-positive breast cancer [22]. A retrospective exploratory analysis of data from the EMILIA clinical trial and primary results from the TH3RESA trial have shown the potential of T-DM1 to improve survival in the subset analysis of patients with CNS metastases at baseline [29, 30]. Results from these clinical trials indicate a potential of these novel HER2-targeting agents for patients with brain metastases. Further studies are warranted to reveal the mechanism of BBB penetration and the effects of these agents on brain metastasis.

Our study has some limitations. First, a retrospective data collection was done for this multi-institutional study. Therefore, the facts that a central laboratory evaluation of histopathological findings was not performed and that the treatment regimen was not standardized might have affected the overall outcomes. Second, the processes of extracranial metastases might have affected patient survival, despite the fact that our previous study revealed that the cause of death in at least 74 % of the HER2-positive patients and 56.7 % of the ER-positive/HER2-positive patients who developed brain metastasis might be related to the brain metastasis itself [5]. Considering this, we believe our results from the largest cohort to date of HER-2-positive breast cancer patients could support the potential use of HER2 targeting agents for brain metastasis in these patients.

Conclusions

Our results showed that HER2-positive patients with more than three brain metastases at the time of diagnosis had a poor prognosis and that regardless of the use of trastuzumab before developing brain metastasis, treatment with both trastuzumab and lapatinib after developing brain metastasis might improve patients survival. Further studies are needed to determine the best treatment strategy, including these HER2-targeting agents, for this patient population.

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Conflict of interest Naoki Niikura belongs to the Endowed Chair Department of Chugai Co. Ltd. Hiroji Iwata has received a honorarium from Chugai Co. Ltd and GlaxoSmithKline. Other authors have no conflicts of interest to declare.

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CLINICAL TRIAL

Anastrozole versus tamoxifen as adjuvant therapy for Japanese postmenopausal patients with hormone-responsive breast cancer: efficacy results of long-term follow-up data from the N-SAS BC 03 trial

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Abstract Aromatase inhibitors are superior to tamoxifen as adjuvant therapy in postmenopausal patients with hormone-responsive breast cancer. We report the follow-up efficacy results from the N-SAS BC 03 trial (UMIN CTRID: C000000056) where anastrozole was compared with tamoxifen as adjuvant therapy in postmenopausal Japanese patients with hormone-responsive early breast cancer. The full analysis set contained 696 patients (anastrozole arm, $n = 345$; tamoxifen arm, $n = 351$). The log-rank test was used to compare the two groups in terms of disease-free survival (DFS) and relapse-free survival (RFS); Kaplan–Meier estimates were calculated. The treatment effects were estimated by Cox's proportional hazards model. To examine time-varying effect of hazard ratios, we estimated time-varying hazard ratios at time t [HR(t)] using data from time t up to 12 months. After a median follow-up of 98.5 months, hazard ratios (95 % CIs) were 0.90 (0.65–1.24; log-rank $p = 0.526$) for DFS and 0.83 (0.56–1.23; log-rank $p = 0.344$) for RFS. Hazard ratios (95 % CIs) for DFS and RFS up to 36 months were 0.69 (0.40–1.17) and 0.54 (0.27–1.06) and those after 36 months were 1.06 (0.70–1.59) and 1.05 (0.64–1.73), respectively. Time-varying hazard ratios for both DFS and RFS showed that hazard ratios were initially in favor of anastrozole and approached 1.0 at around

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36 months. Superior efficacy of anastrozole to tamoxifen suggested by the initial analysis was not confirmed in the present analysis after a long-term follow-up period. Advantage of anastrozole was the greatest immediately after switching from tamoxifen and then decreased thereafter.

Keywords Breast cancer · Adjuvant therapy · Hormonal therapy · Anastrozole · Tamoxifen

Background

Aromatase inhibitors are superior to tamoxifen as adjuvant therapy in postmenopausal patients with hormone-responsive breast cancer in terms of disease-free survival [1–7]. Most clinical trials have been conducted in western countries, and there has been concern regarding possible ethnic differences in the efficacy as well as toxicity of these hormonal agents. The cytochrome P450 (CYP) 2D6 genotype, which metabolizes tamoxifen into its more potent metabolite, endoxifen, and the distribution of the CYP19 gene (aromatase) polymorphisms differ among the Caucasian and Asian population [8]; this may potentially cause differences in the efficacy and safety of aromatase inhibitors between the Caucasian and Japanese populations. Nevertheless, our previous analysis of the N-SAS BC03 study at a median follow-up of 42 months had shown that switching from tamoxifen to anastrozole was probably to decrease disease recurrence when compared with the use of tamoxifen in postmenopausal Japanese patients with breast cancer at a magnitude similar to that observed in the western studies. Notably, we found ethnic differences in major adverse events, which may be attributable to a low baseline risk of such events in Japanese women [9].

The Oxford overview meta-analysis found that approximately 15 % of breast cancer recurrences occurred within the first 5 years after starting tamoxifen, with an incidence of approximately 17 % over the next 10 years, and approximately 9 % of breast cancer mortality occurred within the first 5 years after starting tamoxifen, with an incidence of approximately 18 % over the next 10 years. Thus, most breast cancer recurrences and deaths occurred after 5 years of tamoxifen administration during 15 years of follow-up since diagnosis [10]. Therefore, it is of clinical importance to investigate the long-term follow-up data from a randomized controlled trial of aromatase inhibitors in postmenopausal patients with early breast cancer in Japan.

Hence, here we report the efficacy results from the long-term follow-up data from the N-SAS BC 03 trial (UMIN CTRID: C000000056), in which anastrozole was compared with tamoxifen in postmenopausal patients with hormone-responsive early breast cancer who had taken tamoxifen as adjuvant therapy for 1–4 years during the 5 years of treatment.

Patients and methods

Study design

The details of the original study design as well as statistical considerations have been described elsewhere [9]. In brief, this was a multi-institutional, open-label, randomized control trial designed to compare the efficacy and safety of tamoxifen with those of tamoxifen followed by anastrozole in postmenopausal women with hormone-responsive breast cancer who remained disease-free after having received tamoxifen for 1–4 years as adjuvant therapy. The subjects were randomly assigned to continue receiving tamoxifen (20 mg/day) or to switch to anastrozole (1 mg/day). The total duration of treatment was 5 years. The primary endpoints were disease-free survival (DFS) and adverse events. The secondary endpoints were relapse-free survival (RFS), OS, and the health-related quality of life (HRQOL). At the time of randomization, treatment assignments were adjusted according to the following factors: clinical stage (I, IIA, IIB/IIIA/IIIB), the number of metastases to axillary lymph nodes (0/1–3/>3), HER2 status (unknown/0, 1+, 2+/3+), tumor size (<3/≥3 cm), estrogen receptor (ER) and progesterone receptor (PR) status [ER(+), PR(+)/ER(+), PR(−)/ER(−), PR(+)], type of surgery (breast-conserving surgery/mastectomy), duration of tamoxifen administration (1.0 to <2.0 years/2.0–4.0 years), age (<60 years/≥60 years), chemotherapy (performed/not performed), and institution. Menopause in this study was defined as follows: an age of >60 years, an age of >45 years with amenorrhea for 1 year or longer without hysterectomy, or bilateral ovariectomy.

Out of a total of 706 recruited patients, 696 patients (anastrozole arm, $n = 345$; tamoxifen arm, $n = 351$) were

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Table 1 Patients' characteristics of full analysis set

	ANA $n = 345$	TAM $n = 351$	p value
Age [median (min–max)]	60 (45–77)	60 (44–82)	0.241*
Stage			0.960†
I	142 (41.2)	147 (41.9)	
IIA	126 (36.5)	125 (35.6)	
IIB	52 (15.1)	57 (16.2)	
IIIA	11 (3.2)	11 (3.1)	
IIIB	14 (4.1)	11 (3.1)	
Pathological tumor size			0.943†
<3 cm	274 (79.4)	278 (79.2)	
≥3 cm	71 (20.6)	73 (20.8)	
Nodal status			0.370†
0	203 (58.8)	211 (60.1)	
1–3	102 (29.6)	99 (28.2)	
4–9	23 (6.7)	31 (8.8)	
10-	17 (4.9)	10 (2.8)	
ER			0.932†
Positive	321 (93.0)	326 (92.9)	
Negative	24 (7.0)	25 (7.1)	
PR			0.948†
Positive	271 (78.6)	275 (78.3)	
Negative	74 (21.4)	76 (21.7)	
Type of surgery			0.872†
Breast-conserving surgery	181 (52.5)	182 (51.9)	
Mastectomy	164 (47.5)	169 (48.1)	
HER2			0.988†
0, 1+, 2+	165 (47.8)	168 (47.9)	
3+	13 (3.8)	14 (4.0)	
Unknown	167 (48.4)	169 (48.1)	
Chemotherapy			0.660†
+	164 (47.5)	161 (45.9)	
−	181 (52.5)	190 (54.1)	

* Mann–Whitney U test

† Mantel test

n (%) was shown in all items except for age

used as a full analysis set for the present report. Patients' characteristics for the full analysis set are shown in Table 1. One patient in the anastrozole arm was excluded from the protocol because she experienced recurrence before her allocated protocol treatment was initiated. The consort diagram is shown in Fig. 1.

In the present report, we intended to investigate the efficacy data (DFS and RFS) of the long-term follow-up data as well as the time-varying effect of hazard ratios by the described statistical methods. All of the following were events considered for DFS: locoregional relapse, distant metastasis, asynchronous cancer or secondary cancer (except skin basal cell cancer/spinocellular cancer and uterine intraepithelial cancer), and death from any cause. The data were censored on the day when the above events were last confirmed to be absent or on the day when survival was last confirmed for survivors. Events for RFS were locoregional relapse and distant metastasis. The data were censored on the day when the above events were last confirmed to be absent, on the day of occurrence of asynchronous or secondary cancer, or on the day when none of the above events was confirmed. For patients who died with none of the above events confirmed, data were censored on the date of death.

Statistical methods

For each treatment group, backgrounds were summarized and compared with the Mantel test. The log-rank test was used to compare the two groups in terms of DFS and RFS, and Kaplan–Meier estimates were calculated. The treatment effects were estimated by Cox's proportional hazards model and were expressed as hazard ratios with associated 95 % confidence intervals (CIs). To examine the time-varying effect of hazard ratios [11], we estimated time-varying hazard ratios at time t [HR(t)] using data from time t up to 12 months later. If the proportional hazards' assumption was admissible, these ratios took a nearly constant value.

Results

After a median follow-up of 98.5 months (range, 2.8–134 months), the number of the events related to DFS was 71 in the ANA arm as compared with 77 in the TAM arm; the number of events related to RFS was 46 in the ANA arm as compared with 54 in the TAM arm. The unadjusted hazard ratio was 0.90 (95 % CI 0.65–1.24; log-rank $p = 0.526$) for DFS and 0.83 (95 % CI 0.56–1.23; log-rank $p = 0.344$) for RFS. Kaplan–Meier prevalence curves for DFS and RFS are shown in Figs. 2 and 3, respectively. The distribution of the events is shown in Table 2.

The estimated hazard ratio (95 % CIs) for DFS and RFS until each time point (administrative right censored data) was as follows: until 24 months, 0.46 (0.23–0.91) and 0.47 (0.21–1.05); until 36 months, 0.69 (0.40–1.17) and 0.54 (0.27–1.06); until 48 months, 0.75 (0.48–1.19) and 0.60 (0.34–1.04); until 60 months, 0.82 (0.55–1.24) and 0.69 (0.42–1.14); until 72 months, 0.87 (0.59–1.28) and 0.78 (0.49–1.24); until 84 months, 0.96 (0.68–1.36) and 0.93 (0.61–1.42); until 96 months, 0.89 (0.64–1.25) and 0.87 (0.58–1.31); until 108 months, 0.87 (0.63–1.21) and 0.84 (0.56–1.25); and until 120 months: 0.89 (0.64–1.23) and 0.83 (0.56–1.23), respectively. Hazard ratios (95 % CIs)

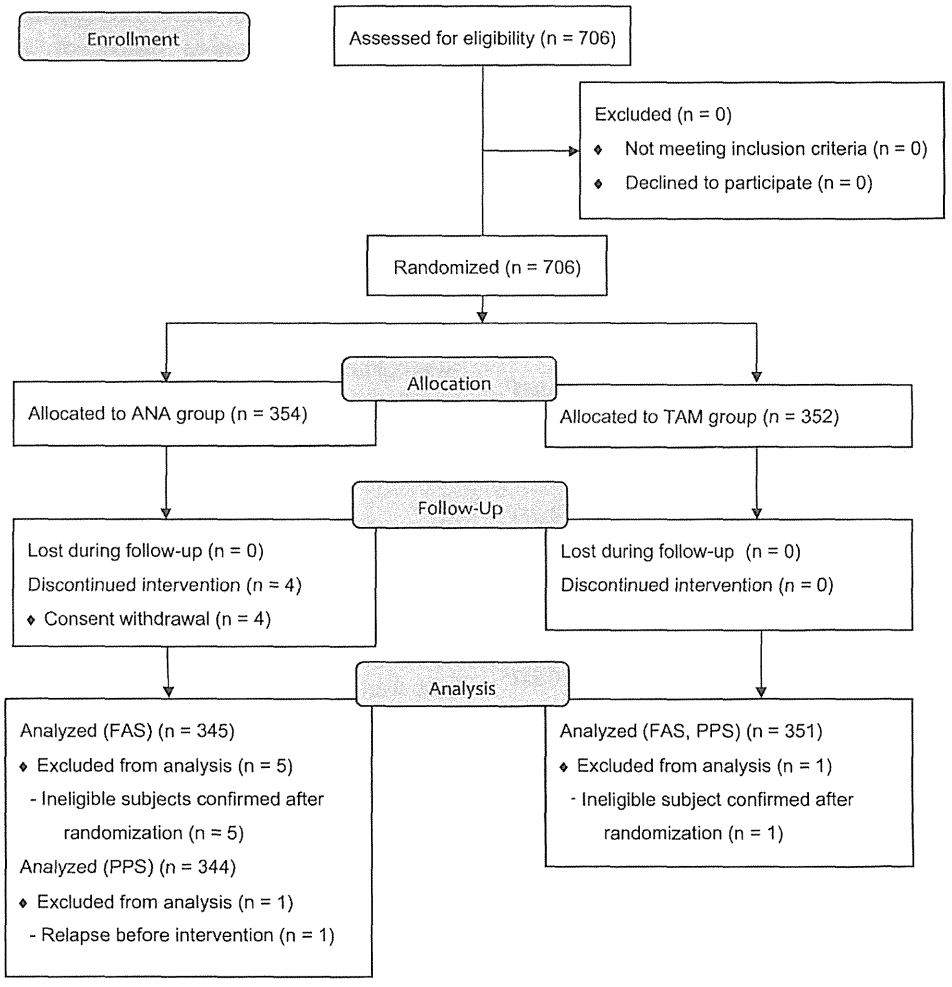


Fig. 1 Consort diagram. *ANA* anastrozole arm, *TAM* tamoxifen arm, *FAS* full analysis set (Patients randomly assigned and started protocol treatment), *PPS* per protocol set (Patient fulfilled the protocol in terms of the eligibility, interventions, and outcome assessment)

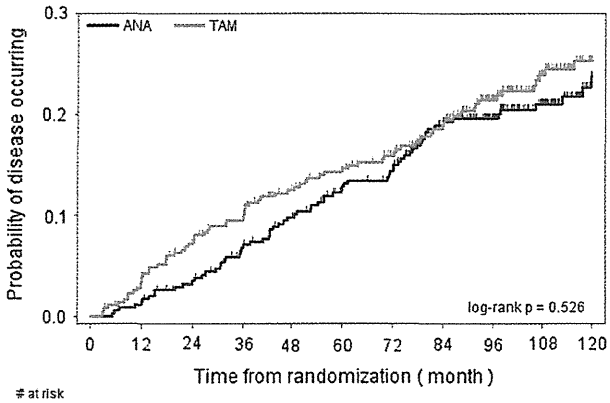
for DFS and RFS until 36 months were 0.69 (95 % CI 0.40–1.17) and 0.54 (95 % CI 0.27–1.06), and those after 36 months were 1.06 (95 % CI 0.70–1.59) and 1.05 (95 % CI 0.64–1.73), respectively. Time-varying hazard ratios for DFS and RFS for anastrozole versus tamoxifen that were described in Figs. 4 and 5, respectively, showed that both of hazard ratios were initially in favor of anastrozole and then approached 1.0 at around 36 months.

No significant difference in the total number of the patients who died of any cause (15 in ANA arm and 22 in TAM arm) was observed between the groups (log-rank $p = 0.210$).

Discussion

The superior efficacy of anastrozole over tamoxifen in Japanese postmenopausal patients with hormone-responsive early breast cancer was suggested by the N-SAS BC03 trial at a median follow-up of 42 months [9]. The number of events included in the previous report was small; therefore, we attempted to investigate if the superior efficacy of anastrozole in the Japanese population could be confirmed by long-term follow-up data, which could accumulate a larger number of events. Although the number of the total events increased from 63 to 148 after a median follow-up of 98.5 months, the hazard ratio of anastrozole over tamoxifen for DFS and RFS increased. When we looked at the data closely, both hazard ratios for DFS and RFS were in favor of anastrozole before 3 years, but they increased to 1.0 after around 3 years; this corresponded to the median treatment period of the protocol therapy. A similar number of events occurred in both arms after cessation of the protocol treatment, and this may have canceled the superior efficacy of anastrozole, which had been suggested during the protocol treatment.

Similar trends in the hazard ratio during the follow-up period have been observed in other clinical trials, which

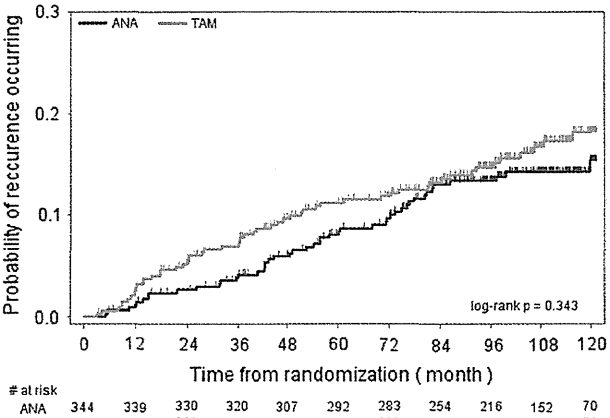


Log-rank test: $p = 0.526$

	HR	(95% CI)	p-value
Allocation (ANA/TAM)	0.90	(0.65–1.24)	0.526
Allocation (ANA/TAM) before 36 months	0.69	(0.40–1.17)	0.169
Allocation (ANA/TAM) after 36 months	1.06	(0.70–1.59)	0.784

ANA = anastrozole, TAM = tamoxifen

Fig. 2 Kaplan–Meier prevalence curves for disease-free survival



Log-rank test: $p = 0.343$

	HR	(95% CI)	p-value
Allocation (ANA/TAM)	0.83	(0.56–1.23)	0.344
Allocation (ANA/TAM) before 36 months	0.54	(0.27–1.06)	0.072
Allocation (ANA/TAM) after 36 months	1.05	(0.64–1.73)	0.835

ANA = anastrozole, TAM = tamoxifen

Fig. 3 Kaplan–Meier prevalence curves for relapse-free survival

compared sequential aromatase inhibitors versus tamoxifen for 5 years. For instance, the hazard ratio of exemestane over tamoxifen in the IES trial at the 30.6-month report was 0.68 [12], at the 55.7-month report was 0.76 [13], and at the 91.0-month report was 0.81 [7]. This trend for the hazard ratio over time does not simply mean that the efficacy of aromatase inhibitors is negated after cessation of treatment.

Table 2 Distribution of the events

Event	ANA ($n = 347$)	TAM ($n = 349$)
Local recurrence	13	20
Distant recurrence	28	31
Primary cancer in the contralateral breast	4	4
Intercurrent death	6	3
Second primary non-breast cancer	20	19
Total	71	77

ANA anastrozole, *TAM* tamoxifen

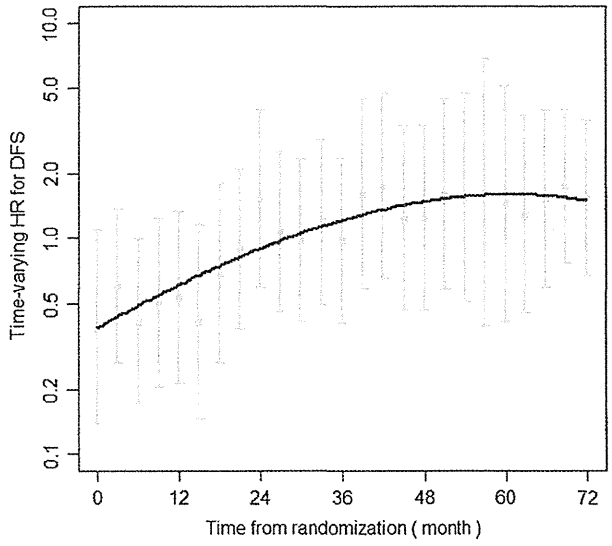


Fig. 4 Time-varying hazard ratios for disease-free survival for anastrozole versus tamoxifen. *Gray lines* show hazard ratio and 95 % confidence interval of each 12 months period and a curve shows cubic-smoothed point estimation of the hazard ratio

Because tamoxifen has retained superior efficacy over no treatment or placebo even after the completion of the 5-year treatment period, which is the so-called "carry-over effect" [10], anastrozole may also have a similar effect as tamoxifen. Some clinical trials have shown that 10 years of hormonal treatment has superior efficacy to 5 years of treatment [14, 15]. Therefore, anastrozole treatment for longer than 5 years could result in better outcomes. Clinical trials evaluating this are ongoing including N-SAS BC 05, which our group conducted (UMIN CTRID: 000000818).

As for overall survival, the total number of the patients who died of any cause was 15 in the ANA arm and 22 in the TAM arm, which did not reach a statistically significant level (log-rank $p = 0.210$). Similar to most other clinical trials that have compared aromatase inhibitors with tamoxifen, even after long-term follow-up, the number of events in this study was so low that we could not conclude whether anastrozole was more efficacious than tamoxifen

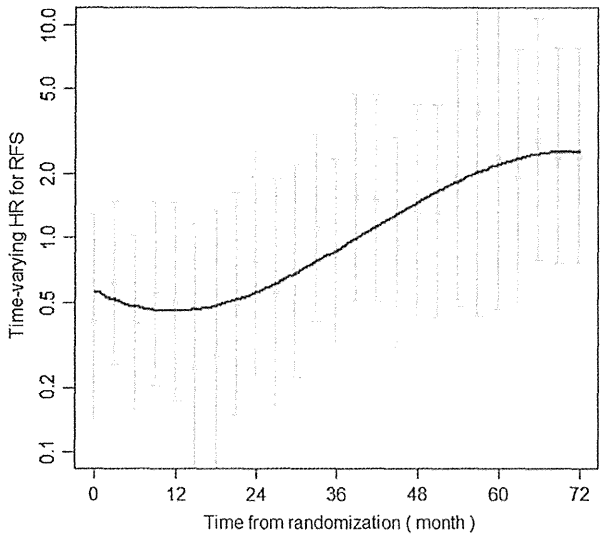


Fig. 5 Time-varying hazard ratios for relapse-free survival for anastrozole versus tamoxifen. *Gray lines* show the hazard ratio and 95 % confidence interval of each 12 months period; a curve shows cubic-smoothed point estimation of the hazard ratio

in terms of overall survival. A meta-analysis of clinical trials would bring conclusive results.

In summary, the efficacy of sequencing from tamoxifen to anastrozole over tamoxifen alone in the Japanese population was investigated over a long-term follow-up period through the N-SAS BC03 trial. The efficacy was the greatest immediately after switching from tamoxifen and then decreased thereafter.

Acknowledgments We thank Yumiko Nomura and her team for the excellent data management. We are indebted to all the patients and the investigators who participated in this trial, especially, to the investigators who have contributed to the data updating listed in the Appendix. This study was funded by the Comprehensive Support Project for Oncology Research (CSPOR) of Public Health Research Foundation. The corporate and individual sponsors of this study are listed on the CSPOR website (http://www.csp.or.jp/cspor/kyousan_e.html). The pharmaceutical manufacturer/distributor who provided financial contribution as a corporate sponsor took no part in this study other than providing information relevant to the proper use of study drugs. All decisions concerning the planning, implementation, and publication of this study were made by the executive committee of this study. This clinical trial complies with the current laws in Japan.

Appendix

K. Aogi (NHO Shikoku Cancer Center), Y. Hozumi (Jichi Medical University Hospital), N. Wada (National Cancer Center Hospital East), C. Egawa (Kansai Rosai Hospital), H. Iwata (Aichi Cancer Center Hospital), Y. Fujiwara (National Cancer Center Hospital), K. Nakagami (Shizuoka General Hospital), M. Takahashi (NHO Hokkaido Cancer Center), T. Ito (Rinku General Medical Center), N. Ogino (Osaka Saiseikai Tondabayashi Hospital), M. Funakoshi (Hiroshima City Asa Hospital), S. Mitsuyama (Kitakyushu Municipal Medical Center), H. Abe (Shiga University of Medical Science), N. Masuda (NHO Osaka National Hospital), H. Tokura (Ashikaga Red Cross Hospital), S. Maeda (NHO Nagasaki Medical Center), S. Kamigaki (Sakai Municipal Hospital), S. Ohno (NHO National Kyushu Cancer Center), H. Yagata (St. Luke's International Hospital), H. Arioka (Yokohama Rosai Hospital), S. Karamatsu (Toyokawa City Hospital), H. Kawaguchi (Matsuyama Red Cross Hospital), A. Fukuuchi (Mitsui Memorial Hospital), T. Sugimoto (Kochi Medical School Hospital), Y. Katayose (Akita City Hospital), N. Yamamoto (Chiba Cancer Center), S. Kuze (Chutoen General Medical Center), M. Okada (Hiroshima University Hospital), H. Matsumoto (Saitama Cancer Center), T. Saito (Saitma Red Cross Hospital), Y. Tokuda (Tokai University Hospital), H. Tomita (Niigata Prefectural Sakamachi Hospital), S. Hojo (Osaka Saiseikai Senri Hospital), R. Nishimura (Kumamoto Municipal Hospital), G. Amano (Nihonkai General Hospital), M. Yoshida (Seirei Hamamatsu General Hospital), Y. Park (Toho University Sakura Medical Center), T. Toyama (Nagoya City University Hospital), Y. Komoike (Kinki University Hospital, Faculty of Medicine), F. Tsukamoto (Osaka Koseinenkin Hospital), T. Kunihisa (Yodogawa Christian Hospital), M. Ochi (Miyoshi Central Hospital), A. Matsui (NHO Tokyo Medical Center), M. Inaba (Kanagawa Cancer Center), S. Nakano (Aichi Medical University Hospital), K. Hashimoto (Shimane Prefectural Central Hospital), H. Doihara (Okayama University Hospital), T. Watanabe (Sendai Medical Center), H. Tahara (The Institute of Medical Science, The University of Tokyo), Y. Tamaki (Osaka Medical Center for Cancer and Cardiovascular Diseases), S. Ozaki (Kochi Prefectural Hata Kenmin Hospital), M. Kitada (Asahikawa Medical University Hospital), K. Kuroi (Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital), M. Iguchi (Kanazawa University Hospital), F. Tanaka (Fukui Red Cross Hospital), N. Sonoda (Yurin Koseikai Fuji Hospital), A. Naito (Nagoya Kyouritsu Hospital), K. Kobayashi (Kinki Central Hospital), Y. Maehara (Kyushu University Hospital), M. Hashimoto (Iizuka Hospital), H. Kimura (Okayama Saiseikai General Hospital), S. Imoto (School of Medicine Kyorin University), T. Ri (Kyoto First Red Cross Hospital), S. Hara (Sasebo Municipal General Hospital), K. Okada (Uwajima City Hospital), J. Ando (Tochigi Cancer Center), K. Sakakibara (Nagoya City West Medical Center), M. Kuranami (Yamato Municipal Hospital)

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ORIGINAL ARTICLE

Tamoxifen plus tegafur-uracil (TUFT) versus tamoxifen plus Adriamycin (doxorubicin) and cyclophosphamide (ACT) as adjuvant therapy to treat node-positive premenopausal breast cancer (PreMBC): results of Japan Clinical Oncology Group Study 9404

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Abstract
Purpose A prospective randomized clinical trial was conducted to evaluate the efficacy of tamoxifen plus doxorubicin and cyclophosphamide compared to tamoxifen plus tegafur-uracil as an adjuvant therapy to treat node-positive premenopausal breast cancer (PreMBC).
Methods Eligibility criteria included pathologically node-positive (n = 1–9) preMBC with curative resection, in stages I–IIIA. Patients were randomized to receive either tamoxifen 20 mg/day plus tegafur-uracil 400 mg/day (TU) for 2 years or six courses of a 28-day cycle of doxorubicin 40 mg/m^2 plus cyclophosphamide 500 mg/m^2 on day 1 along with tamoxifen (ACT) given for 2 years as adjuvant therapy. Primary endpoint was overall survival (OS), and secondary endpoint was recurrence-free survival (RFS).
Results In total, 169 patients were recruited (TU arm 87, ACT arm 82) between October 1994 and September 1999. The HR for OS was 0.76 (95 % CI 0.35, 1.66, log-rank p = 0.49) and that for RFS was 0.77 (95 % CI 0.44, 1.36, log-rank p = 0.37), with ACT resulting in a better HR. The 5-year OS was 79.7 % for patients in the TU arm and 83 % for those in the ACT arm. The 5-year RFS was 66.1 % for patients in the TU arm and 70.6 % for those in the ACT arm. A higher proportion of patients in the ACT arm experienced grade 3 leucopenia (0 % in the TU arm, 4 % in the ACT arm).
Conclusions There were no significant differences in the efficacy of TU and ACT as adjuvant therapy.

Keywords Breast cancer · Adjuvant treatment · Node-positive · Premenopausal

On behalf of the JCOG Breast Cancer Study Group.

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Introduction

Progression-free survival and overall survival have been improved according to the development of postoperative adjuvant therapy using drugs based on clinical trials. Prior to the 1980s, cyclophosphamide, methotrexate, and fluorouracil (CMF) therapy was the standard therapy, but development of Adriamycin in the 1990s indicated that Adriamycin might surpass CMF in terms of prolonging prognosis. Prior to the 1990s, oral anticancer agents became the standard therapy since they were thought to cause fewer adverse events in Japan.

Combined administration of oral fluoropyrimidine plus tamoxifen for 2 years postoperatively was reported to result in a high 5-year survival of 91 % for patients with Stage II breast cancer and 78 % for those with Stage III breast cancer [1, 2], and combined administration of oral fluoropyrimidine plus tamoxifen was reported to diminish QOL less [1]. The criteria for determination of estrogen receptor (ER) status at the time differed from the current criteria, and tamoxifen was supposed to be less efficacious in ER-negative patients. However, tamoxifen was administered regardless of the patient's ER status in general. Moreover, the form of administration was typically in combination with an anticancer agent including chemotherapy and hormone therapy. This study was planned within this context.

Current postoperative drug therapy to treat breast cancer is often chosen depending on the breast cancer subtype, which is determined based on panels for markers such as ER, HER2, and Ki67 [2]. This selection is based on predicted drug efficacy. The fact that lymph node metastasis is a prognostic factor was true when this trial began and it remains true today. When numerous lymph node metastases are noted, standard therapy is the administration of anthracycline and taxane, regardless of the cancer subtype. This study sought to assess the superiority of Adriamycin and cyclophosphamide (AC) + tamoxifen (ACT regimen) over oral tegafur-uracil (UFT) + tamoxifen (TU regimen), which was the standard therapy in Japan when the trial began, as a postoperative adjuvant therapy to treat premenopausal breast cancer in patients who were histopathologically confirmed to have lymph node metastasis. This trial also sought to determine whether all patients with node-positive breast cancer needed to be administered anthracycline or whether administration of oral fluoropyrimidine was sufficient.

Patients and methods

Eligibility and excluding criteria

Premenopausal female patients over the age of 15 with Stage I–IIIa breast cancer were eligible for this study. All patients had to have undergone curative mastectomy with axillary node dissection, and a histological examination had to reveal involvement of 1–9 axillary nodes. Other eligibility criteria were a World Health Organization (WHO) performance status of 0–1, adequate bone marrow and liver and kidney function, and no evidence of metastasis. Patients who received previous systemic treatment for breast cancer were excluded. The informed consent of each patient was obtained before study participation.

Planned treatment schedules

All patients randomized to TU or ACT regimen. For patients in the TU arm, tamoxifen (20 mg/day) and UFT (400 mg/day) were administered for a maximum of 2 years in all patients. For patients in the ACT arm, Adriamycin (40 mg/m^2 intravenously) and cyclophosphamide (500 mg/m^2 intravenously) were administered on day 1 every 28 days. This cycle was repeated six times. Tamoxifen (20 mg/day) was administered for a maximum of 2 years in all patients, regardless of hormonal receptor status.

Randomization was done using the minimization method, and the arms were balanced with regard to ER and progesterone receptor (PR) status (either one positive (>10 %) versus both negative and unknown), HER2 status (positive versus negative or unknown), number of metastatic nodes (1–3 versus 4–9), and institution.

Patient assessment

Initial workup included medical history, tumor assessment, physical examination, routine hematology and chemistry test, chest radiography, liver ultrasonography, and a bone scan. Hematology and chemistry tests, tumor marker measurements, and urinalysis were repeated monthly. To check for distant metastasis, a chest radiography and liver ultrasonography were performed every 6 months, a bone scan was performed every year, and bilateral mammography was performed every 2 years. Hematological disorders and toxicity were evaluated according to the Toxicity Grading Criteria of the Japan Clinical Oncology Group (JCOG) [3] and were recorded on case report forms.

Study endpoint

The primary endpoint of this study was overall survival (OS), and the secondary endpoint was recurrence-free survival (RFS). OS was defined as the time from randomization to death from any cause, and it was censored as of the date of final follow-up. RFS was defined as the time from randomization to either the first incidence of recurrence or death from any cause, and it was censored as of the date of final follow-up. OS and RFS were evaluated according to hormone receptor status (either ER- or PR-positive versus both ER- and PR-negative or unknown) in subgroup analyses. In addition, the safety of treatment was evaluated.

Statistical analysis plan

If patients treated with ACT had a significantly longer OS than patients treated with TU, then ACT would be