

Table 4 Characteristics of second-line ET responders who had initial resistance to first-line ET

N	Menopause status	First line ET			Second line ET		
		Drug	Best response	Duration (month)	Drug	Best response	Duration (month)
1	Post	LTZ	PD	4.6	TAM	PR	15.8
2	Post	ANZ	PD	4.5	TAM	LSD	7.3
3	Pre	TAM/ LHRHa	PD	3.9	MPA	PR	6.6
4	Post	ANZ	PD	1.8	TAM	LSD	14.8

ET endocrine therapy, LTZ letrozole, ANZ anastolozole, TAM tamoxifen, LHRHa luteinizing hormone-releasing hormone analog, PD progressive disease, PR partial response, LSD stable disease more than 6 months

We have initially investigated known prognostic factors by use of multivariate Cox regression analysis. PgR and other potential biomarkers predictors of endocrine resistance will be examined in validation studies. Notably, stage IV breast cancer provides an optimum setting for such translational research because serial tissue sampling of the primary tumor may be readily achieved.

This study had some limitations inherent in retrospective analyses. First, we used three kinds of antibody to detect PgR expression of the tumor and two kinds of systems to detect HER2 expression. Results from every antibody or system were indicative of significant differences in our analysis, however. Second, we did not perform imaging studies every fixed period because this study was performed in a clinical practice setting. Therefore, we may have not estimated the CBR exactly.

In conclusion, we suggest PgR and clinical benefit as prognostic markers for patients with stage IV hormone receptor-positive primary metastatic breast cancer. In addition, we emphasize the evidence that some patients might benefit from second-line ET even after failure of first-line ET.

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Paclitaxel-induced peripheral neuropathy in patients receiving adjuvant chemotherapy for breast cancer

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Abstract

Background The long-term outcomes and risk factors of paclitaxel-induced peripheral neuropathy (PIPN) have not yet been fully elucidated.

Methods We identified 219 breast cancer patients who received paclitaxel as adjuvant chemotherapy between 2002 and 2009. We retrospectively analyzed the incidence, time to onset, duration, and risk factors for PIPN by chart review.

Results Of the 219 patients, 212 developed PIPN (97%) during a median follow-up time of 57 months (range 5.3–95.5). Median time to PIPN onset was 21 days (range 11–101) for the entire patient population: 35 days (range 14–77) for weekly administration and 21 days (range 11–101) for tri-weekly administration. PIPN caused termination of paclitaxel treatment in 7 patients (4%). Median duration of PIPN was 727 days (range 14–2621 days). PIPN persisted in 64 and 41% of patients at 1 and 3 years after initiating paclitaxel, respectively. Age ≥ 60 years and severity of PIPN were significantly associated with PIPN duration.

Conclusions PIPN persists longer in older patients and in those who experience severe neuropathy. Further studies to identify the risk factors for PIPN are warranted.

Keywords Breast cancer · Paclitaxel · Peripheral neuropathy

Introduction

Paclitaxel (PTX) is a key component of many therapeutic regimens in both early-stage and metastatic breast cancer [1–4]. PTX, a microtubule-stabilizing agent, binds to microtubules and abolishes their dynamic behavior, leading to inhibition of cell proliferation [5]. The agent is known to cause peripheral neurotoxicity (PN), which may result in discontinuation of treatment and poor quality of life.

The incidence of PTX-induced PN (PIPN) is known to depend on several factors, including dosages per cycle, treatment schedule, duration of infusion, cumulative dosage, and co-morbidity such as diabetes [6–11]. Although the clinical response of tumors to PTX is an important factor in selecting a chemotherapy regimen, it is also prudent to evaluate the risk of developing PN associated with each regimen, especially for patients already at high risk for neuropathy. The risk of sensory neuropathy is proportional to the dose of PTX administered. Grade 3 or 4 sensory neurotoxicity occurs in 20–35% of patients receiving 250 mg/m² every 3 weeks compared to 5–12% using doses ≤ 200 mg/m² every 3 weeks [12]. The weekly schedule is associated with higher neurotoxicity than the tri-weekly schedule. In a previous study, grade 3 neuropathy occurred significantly more often with the weekly regimen than with the tri-weekly regimen (24 vs. 12%) [13]. In another study, which compared weekly versus

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tri-weekly PTX dosages, it was reported that grade 2, 3, or 4 neuropathy occurred more frequently with weekly than with tri-weekly PTX administration (27 vs. 20%, respectively) [14].

The time to onset of PIPN was previously determined in a phase III trial of patients with metastatic breast cancer treated with PTX (175 mg/m²) every 3 weeks; the mean total dose at the onset of grade 2 neurotoxicity was 715 mg/m² [15]. However, there are limited data available describing the outcome of PIPN and risk factors of severe PN. We therefore conducted a retrospective study to determine the duration of PIPN and to identify potential factors predicting severe or persistent PN.

Patients and methods

Data collection

This study included breast cancer patients treated with PTX as adjuvant chemotherapy at the National Cancer Center Hospital between 2002 and 2009. All patients met the following criteria: female gender; age >18 years; recipients of lumpectomy or mastectomy; and presentation of more than one axillary lymph node metastasis, as determined pathologically. The following patients were excluded from this study: those previously treated with PTX, those who presented with severe neuropathy before initiating PTX treatment, and those who discontinued PTX treatment after only 1 cycle for any reason.

We performed chart reviews for all patients to obtain the following information: age; gender; stage; hormonal status; human epidermal growth factor receptor-2 (HER2) status; previous surgical procedures (lumpectomy or mastectomy); adjuvant chemotherapy; adjuvant radiotherapy; PTX administration schedule; date of the first documentation of PIPN; maximum grade of PIPN; date of disappearance of PIPN symptoms. This study was approved by the local institutional review board.

Treatment schedule

Chemotherapy consisted of anthracycline followed by PTX regimens as generally recommended for high-risk breast cancer patients, according to the St. Gallen risk criteria at our division [16, 17]. However, therapeutic options could vary based on the physician's discretion. Patients received either 80 mg/m² of PTX on days 1, 8, and 15 of each 21-day interval for 4 cycles, following anthracycline plus cyclophosphamide (AC) (weekly administration schedule), or 175 mg/m² of PTX on day 1 of each 21-day interval for 4 cycles, following AC (tri-weekly administration schedule).

Grading of PIPN

Patients were evaluated during and after chemotherapy by medical oncologists. We graded PIPN retrospectively according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 3.0 [18]. Grade 1 PIPN had paresthesias including tingling, but not interfering with function, while grade 2 had sensory alterations or paresthesias interfering with function but not interfering with activities of daily living (ADL). Grade 3 had sensory alterations or paresthesias interfering with ADL. Patients were determined to have PIPN if their score for sensory neuropathy was grade 1 or higher. The severity of pain was not evaluated in this study because of insufficient data.

Statistical analysis

The time to onset of PIPN was defined as the time from the date of PTX administration to the date of the first documentation of PIPN. The duration of PIPN was defined as the time from the date of first documentation of PIPN to the date of disappearance of the PIPN symptoms described. The time to onset and duration of PIPN were estimated by the Kaplan–Meier method. We used multivariate Cox regression analysis to identify the variables associated with the time to onset and duration of PIPN. Furthermore, to identify the risk factors for PIPN above grade 2, we applied multivariate logistic regression analysis. A 2-sided $P < 0.05$ was considered statistically significant. All analyses were performed by SAS software, version 9.2 (SAS Institute, Cary, NC, USA).

Results

Patient characteristics

Of the 227 patients initially identified, 2 were excluded due to severe neuropathy induced by combination chemotherapy with AC before being treated with PTX. Several patients discontinued systemic therapy before completion of 1 cycle due to the following adverse events: severe liver dysfunction (grade 3) ($n = 3$), acute renal failure (grade 3) ($n = 1$), allergic reaction (grade 3) ($n = 1$), and interstitial pneumonitis (grade 3) ($n = 1$). Finally, a total of 219 patients were included; 212 patients (97%) developed PIPN which was characterized by numbness and tingling, while 7 had no PIPN symptoms. The maximum severity of PIPN reached in each of the 212 patients was as follows: grade 1, 159 patients (75%); grade 2, 45 patients (21%); and grade 3, 9 patients (4%). Two patients needed dose modifications due to PIPN above grade 2. No patients postponed or skipped the scheduled PTX due to PIPN.

Baseline characteristics of the population are listed in Table 1. The median age of patients was 53 years (range 22–70). Eighteen patients had diabetes mellitus without neuropathy complications at baseline. Disease-free survival and overall survival were evaluated with a median follow-up time of 57.1 months (range 5.3–95.5). A total of 25 patients received weekly PTX: 23 following AC and 2 without AC. The remaining 194 patients received tri-weekly PTX: 182 following AC and 12 without AC. The mean dose intensity was 58 mg/week (range 16–80). Treatment cessation was deemed necessary in 9 patients (4%); reasons for cessation were PIPN (8 patients, 3 with

grade 1, 1 with grade 2, and 5 with grade 3) and myelosuppression (1 patient).

PIPN development time

The median time taken for the total patient group to develop PIPN was 21 days (range 11–101) (Fig. 1). With weekly administration of PTX, the median time taken to develop PIPN was also 21 days (range 11–101); the median time with tri-weekly administration was 35 days (range 14–77).

Cumulative dose

The mean cumulative dose at the onset of grade 1 or higher PIPN was 175 mg/m² for patients treated with PTX every 3 weeks and 320 mg/m² for weekly PTX patients.

Diabetes mellitus

Of 18 diabetic patients, all had PIPN and 3 had maximum grade 3 PIPN. Median time to PIPN onset was 21 days (range 20–21), and median duration of PIPN was 287 days (range 70–503). In patients without diabetes, median time to PIPN was 21 days (range 20–21), and median duration of PIPN was 231 days (range 190–271).

Risk factors correlated with PIPN

Multivariate analysis using a logistic regression model after stepwise selection revealed no significant correlations between time to PIPN onset and maximum PIPN severity (Table 2), while there were significant correlations between duration of PIPN and age (>60 years old) ($P = 0.027$) and between duration of PIPN and maximum PIPN severity ($P = 0.015$) (Table 3). Moreover, we could not identify

Table 1 Patient characteristics

Variables	triPTX (<i>N</i> = 188)	wPTX (<i>N</i> = 24)	All (<i>N</i> = 212)
Age			
Median (range)	53 (22–70)	52 (32–68)	53 (22–70)
<60 (%)	141 (75.0)	17 (70.8)	158 (74.5)
≥60 (%)	47 (25.0)	7 (29.2)	54 (25.5)
Sex (%)			
Female	187 (99.5)	24 (100.0)	211 (99.5)
Male	1 (0.5)	0 (0.0)	1 (0.5)
Lymph (%)			
<4	118 (62.8)	12 (50.0)	130 (61.3)
≥4	70 (37.2)	12 (50.0)	82 (38.7)
Tumor size (%)			
<5 cm	153 (81.4)	18 (75.0)	171 (80.7)
≥5 cm	35 (18.6)	6 (25.0)	41 (19.3)
Surgery (%)			
Mastectomy	114 (60.3)	16 (66.7)	130 (61.3)
Lumpectomy	73 (39.2)	8 (33.3)	81 (38.2)
Excisional biopsy	1 (0.5)	0 (0.0)	1 (0.5)
Systemic therapy (%)			
Chemo	56 (29.8)	8 (33.3)	64 (30.2)
Chemo + endocrine	132 (70.2)	16 (66.7)	148 (69.8)
Radiation (%)			
No	69 (36.7)	8 (33.3)	77 (36.3)
Yes	119 (63.3)	16 (66.7)	135 (63.7)
Hormone (%)			
Negative	48 (25.5)	5 (20.8)	53 (25.0)
Positive	140 (74.5)	19 (79.2)	160 (75.0)
HER2 (%)			
Negative	156 (83.0)	16 (66.7)	172 (81.1)
Positive	32 (17.0)	8 (33.3)	40 (18.9)
Diabetes mellitus (%)			
No	171 (91.0)	23 (95.8)	194 (91.5)
Yes	17 (9.0)	1 (4.2)	18 (8.5)

triPTX tri-weekly paclitaxel, wPTX weekly paclitaxel, chemo chemotherapy

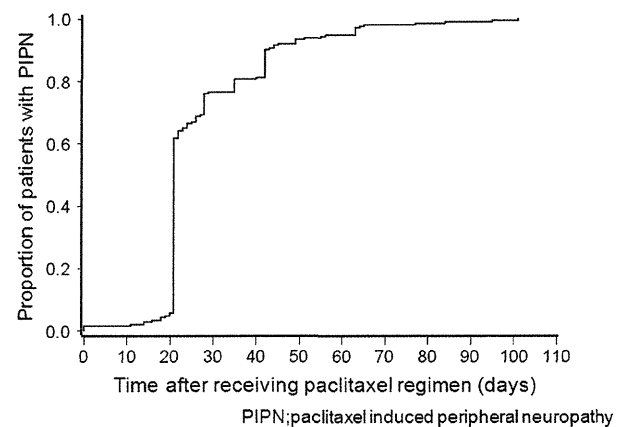


Fig. 1 Time taken for the total patient group to develop paclitaxel-induced peripheral neuropathy

Table 2 Multivariate analysis for factors associated with time to PIPN

Variables	HR	95% CI		P value
Regimen				
triPTX	1			
wPTX	0.66	0.43	1.03	0.070
Age				
<60				
≥60	0.99	0.72	1.37	0.960
Lymph				
<4				
≥4	1.20	0.82	1.77	0.341
Tumor size (cm)				
<5				
≥5	0.98	0.68	1.42	0.917
Radiation				
No				
Yes	0.78	0.51	1.20	0.259
Surgery				
Mastectomy				
Lumpectomy	1.08	0.75	1.56	0.666
Endocrine				
No				
Yes	0.87	0.65	1.18	0.366
Grade				
1				
2 or 3	1.35	0.97	1.87	0.073
Diabetes mellitus				
No				
Yes	1.34	0.81	2.21	0.260

PIPn paclitaxel-induced peripheral neurotoxicity, triPTX tri-weekly paclitaxel, wPTX weekly paclitaxel, HR hazard ratio, CI confidence interval

any correlation with grade 2/3 PIPN (Table 4). Based on the results of multivariate analyses, there were no significant associations between diabetes mellitus and time to PIPN onset ($P = 0.260$) or duration of PIPN ($P = 0.345$) or grade 2/3 PIPN ($P = 0.229$).

Duration of PIPN

The median duration of PIPN was 727 days for the total patient group (range 14–2621) (Fig. 2). With weekly administration, the median duration was not reached (range 14–1089); the median duration for patients with tri-weekly administration was 651 days (range 23–2621). One year after initiating PTX treatment, PIPN (all grades included) persisted in 64% of patients; 3 years after treatment initiation, this number had dropped to 41%.

Table 3 Multivariate analysis for factors associated with duration of PIPN

Variables	HR	95% CI		P value
Regimen				
triPTX	1			
wPTX	0.48	0.19	1.21	0.119
Age				
<60				
≥60	0.55	0.32	0.94	0.027
Lymph				
<4				
≥4	0.86	0.46	1.59	0.621
Tumor size (cm)				
<5				
≥5	1.03	0.59	1.77	0.927
Radiation				
No				
Yes	1.05	0.52	2.12	0.900
Surgery				
Mastectomy				
Lumpectomy	0.67	0.36	1.26	0.213
Endocrine				
No				
Yes	1.10	0.70	1.73	0.668
Grade				
1				
2 or 3	0.53	0.32	0.88	0.015
Diabetes mellitus				
No				
Yes	0.66	0.28	1.56	0.345

PIPn paclitaxel-induced peripheral neurotoxicity, triPTX tri-weekly paclitaxel, wPTX weekly paclitaxel, HR hazard ratio, CI confidence interval

Discussion

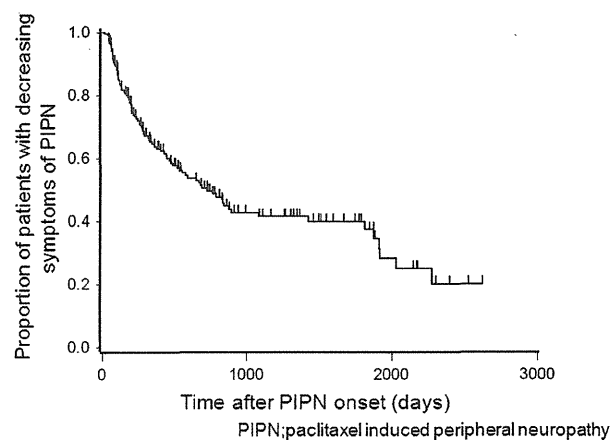
This is the first published report to our knowledge that investigates the time to onset and duration of PIPN among breast cancer patients and explores potential risk factors related to severe and/or persistent PIPN. The data from this study confirm that most patients (97%) developed PIPN with a severity of at least grade 1. Peripheral neuropathy persisted in 64% of patients at 1 year and 41% at 3 years after the first administration of PTX. Approximately half of the patients who received PTX and developed PN experienced recovery from PN within 9 months after cessation of PTX treatment. We found correlations between the maximum PIPN severity and both the time to onset of PIPN and the duration of PIPN. In addition, we observed that PN lasted significantly longer in patients >60 years of age.

Table 4 Multivariate analysis for factors associated with grade 2 or 3 PIPN

Variables	Odds ratio	95% CI	P value
Regimen			
triPTX	0.57	0.18–1.83	0.345
wPTX			
Age			
<60	1.65	0.81–3.36	0.171
≥60			
Lymph			
<4	0.98	0.40–2.41	0.968
≥4			
Tumor size (cm)			
<5	0.47	0.18–1.24	0.125
≥5			
Radiation			
No	0.98	0.35–2.77	0.975
Yes			
Surgery			
Mastectomy	0.73	0.29–1.82	0.499
Lumpectomy			
Endocrine			
No	0.72	0.36–1.45	0.360
Yes			
Diabetes mellitus			
No	2.05	0.69–6.09	0.197
Yes			
Dose intensity			
<58	1.00	0.50–2.01	1.000
≥58			
Cumulative dose			
<700	0.31	0.08–1.13	0.077
≥700	0.57	0.18–1.83	0.345

PIPN paclitaxel-induced peripheral neurotoxicity, triPTX tri-weekly paclitaxel, wPTX weekly paclitaxel, CI confidence interval

Previous studies have reported that the incidence of PIPN is related to several risk factors, including treatment schedule, doses per course, patient age, diabetes mellitus, and cumulative dose [6–11]. We found no association between the severity of PIPN and the PTX administration schedule including single dose, dose intensity, diabetes mellitus, or interval of administration. In our study, the mean cumulative dose at the onset of grade 1 or higher PN was 175 mg/m² for patients treated with PTX every 3 weeks and 320 mg/m² for weekly PTX patients. In contrast to an earlier study [14], our clinical outcomes indicated that tri-weekly administration of PTX was associated with more severe PIPN than weekly administration. However, this result may be attributed to frequent hospital

**Fig. 2** Time to resolving PIPN from the time of developing paclitaxel-induced peripheral neuropathy

visits and/or the relatively small number of patients treated by weekly PTX.

Previous reports suggest there are several risk factors for PIPN, including concurrent administration of cisplatin [19] and various genetic predispositions for neuropathy, such as *Wlds* (slow Wallerian degeneration gene) and *CYP3A* genotype [20, 21], but we did not examine any of those risk factors in this study.

Axonal microtubules are composed largely of β -tubulin. Neurotoxicity is caused by disruption of the microtubule structure, impairing axoplasmic transport and leading to dying-back neuropathy [22]. The most widely accepted mechanism of taxane neurotoxicity is a dying-back process that starts from distal nerve endings and progresses to affect Schwann cells, neuron bodies, or axons, resulting in transport changes that disturb cytoplasmic flow in the affected neurons [23]. Another possible cause of PIPN is that sensory nerves may be particularly vulnerable to the inhibition of tubulin assembly, as sensory nerves have long axons. However, motor neurons and C-neurons are not as sensitive to taxanes as are sensory nerves, despite the fact that these neurons are as long as sensory nerves. Some reports suggest that induction of *Ca α 2 δ -1* expression by PTX in the spinal root may be important, but further investigation is necessary to understand the mechanisms of PIPN [24].

There are no medications that prevent or relieve PIPN. Likewise, there are no laboratory tests that can predict the severity of PN. Management of PIPN is now based on early detection during chemotherapy to prevent its progression to grade 3 or 4. Clinical assessment, including a physical examination, is currently the most reliable method of assessing PIPN because we lack more reliable objective methods, and the symptoms of PIPN, such as numbness, sensory pain, fatigue, and weakness, are complicated [12, 25]. If grade 2 PN is diagnosed, it may be prudent to

withhold PTX until PN improves to at least grade 1; PTX administration can then be resumed at a reduced dose.

There were several limitations to our study. We used physician-based assessments, which relies on patients' report and examiners' interpretation and could have resulted in underestimation and under-reporting of the frequency and severity of PN [26]. In addition, physicians were more prone to quit following symptoms periodically once patients recovered from maximum PIPN. In fact, there were many censored cases in this study (Fig. 2). Therefore, features of PIPN such as location, presence of accompanying symptoms, and triggers for increase or decrease in severity were unclear. This study was retrospective, with censored data; the neurotoxicity corresponding to each grade of PIPN was unclear. In fact, time to onset of PIPN was faster for grades 2 and 3 than grade 1. In order to properly evaluate the correlation between severity and duration of PIPN, we will need further studies to determine whether or not the duration of PIPN is longer when the maximum severity increases from grade 1 to grade 2.

In conclusion, we analyzed the incidence and duration of PIPN and identified correlations between these and several risk factors. We found that the median time to onset of PIPN was 21 days, and the median duration of PIPN was 727 days. Patient age and PIPN severity were the independent risk factors significantly associated with longer PIPN duration. Urgent needs currently include identification of specific risk factors for PIPN, establishment of subjective methods for evaluating PIPN, and development of effective strategies for prevention and treatment of PIPN. To meet these ends, further investigation of the biological mechanisms leading to PIPN is warranted.

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Conflict of interest The authors have declared no conflicts of interest.

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Final Results of a Safety and Efficacy Trial of Preoperative Sequential Chemoradiation Therapy for the Nonsurgical Treatment of Early Breast Cancer: Japan Clinical Oncology Group Study JCOG0306

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Key Words

Clinical trial · Doxorubicin · Early stage breast cancer · Paclitaxel · Preoperative chemotherapy · Radiation therapy

Abstract

Objective: To explore the possibility of nonsurgical treatment of primary breast cancers by a sequential treatment of chemotherapy and radiotherapy. **Methods:** We conducted a safety and efficacy trial of chemotherapy and radiation therapy sequentially as primary therapy in patients with stage I–IIIA breast cancer. All patients underwent mastectomy or lumpectomy 12–16 weeks after the completion of radiation therapy to maximize the effect of radiation therapy. The primary endpoint was the pathological complete response (pCR) rate. **Results:** Between June 2004 and April 2005, one hundred eight patients were enrolled. Thirty six percent of the entire population achieved a pCR, which could not reject the null hypothesis. The pCR rate was 57% in patients with hormone receptor (HR)-negative/HER-2-positive tumors and 52% in patients with triple-negative tumors. While 7% of the HR-negative/HER2-positive patients recurred, a high-

er incidence of recurrence (24%) was observed in triple-negative tumors in a follow-up of 4.5 years. The rate of breast-conserving surgery was 88.9% (96/108). **Conclusion:** The pCR rate was not high enough, even though preoperative sequential chemoradiation therapy did not increase the risk of operative complications and could achieve a high rate of breast-conserving surgery.

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Introduction

Radical mastectomy, which was brought to completion by William S. Halsted [1] in the latter half of the 19th century, was regarded as the standard therapy for primary breast cancer for around a century thereafter. In the 1970s and later, limited operations such as modified radical mastectomy and breast-conserving surgery spread [2, 3]. In the 1980s, inoperable locally advanced breast cancer cases were first treated with anticancer agents, followed by surgical extirpation of reduced tumors. Namely, preoperative or neoadjuvant chemotherapy was performed in order to ren-

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der inoperable cases operable [4]. In the latter half of the 1990s, this therapeutic strategy was extended to operable breast cancer cases in an attempt to improve the breast conservation rate. A number of randomized trials comparing preoperative and postoperative chemotherapies demonstrated that preoperative chemotherapy was comparable to postoperative chemotherapy in terms of survival, and that it was superior in terms of the breast conservation rate [5–8]. Preoperative chemotherapy has thus been ranked among the standard therapies for primary breast cancer.

Preoperative radiotherapy has also been performed since the 1980s, aimed at improving the breast conservation rate and local control. The breast conservation rate had so far improved up to 10–20% with a radiation dose of 45–50 Gy plus a boost of 10 Gy, but the pathological complete response (pCR) rate was still unsatisfying at 5% or so [9]. Limited operation has been supported by the progression of medical as well as radiation therapy before and after surgery. In clear view of this trend, it is considered a future task of clinical oncology of breast cancer to investigate whether ‘nonsurgical therapy’ such as medical or radiation therapy can be substituted for surgery in appropriate cases. Therefore, we investigate in this study whether preoperative chemoradiation therapy can achieve a high pCR rate. If the pCR rate is proven to be high enough, we can consider introducing nonsurgical treatment as a test regimen in future studies.

Patients and Methods

Patient Population

This multicenter, open-label, single-arm, phase II clinical trial was conducted at 29 institutions throughout Japan. The protocol was reviewed and approved by the JCOG Clinical Trial Review Committee and the institutional review board of each participating institution.

Patients were included in this trial if they met all of the following criteria: (1) core needle biopsy-proven invasive breast cancer (female only); (2) clinical stage I–IIIA (UICC/TNM system 1997); (3) tumor diameter of 2–5 cm confirmed by breast ultrasound sonography; (4) existence of all tumors within the planning target volume of the boost radiation, if multifocal lesions exist in the same breast; (5) patients without bilateral breast cancer (metachronous contralateral breast cancer was allowed); (6) age between 20 and 70 years; (7) ECOG performance status of 0 or 1; (8) no previous treatment with chemotherapy or radiotherapy; (9) adequate organ function [absolute neutrophil count (ANC) $\geq 1,500/\text{mm}^3$, platelet count $\geq 100,000/\text{mm}^3$, serum creatinine $\leq 1.5 \text{ mg}/100 \text{ ml}$, GPT (ALT) $\leq 60 \text{ IU/l}$, and total bilirubin $\leq 1.5 \text{ mg}/100 \text{ ml}$], and (10) written informed consent.

Patients were excluded if they met any of the following criteria: (1) current history of malignant neoplasms except for curative carcinoma in situ or mucosal carcinoma, (2) pregnant or lactating women or women with an intention to bear children, (3) active in-

fectious disease, (4) past history of an allergic reaction to cremophor EL (polyoxethylated castor oil) or polysorbate, (5) interstitial pneumonia or fibroid lung revealed by chest X-ray, (6) poorly controlled or insulin dependent diabetes mellitus, and (7) psychological disease or psychological symptoms that interfered with entering this trial.

Endpoints

The primary endpoint was the pCR rate. The secondary endpoints were adverse events, clinical response rate, rate of breast-conserving surgery, relapse-free survival (RFS), and overall survival (OS).

The pCR is designated to include patients with complete disappearance of tumor cells or noninvasive tumor residues in the breast after protocol treatment, regardless of axillary lymph node metastasis. The pCR was assessed by the central review board, consisting of three pathologists, on a representative slice of surgical specimen which is determined by local site pathologists. Hematoxylin and eosin (H&E)-stained slides were prepared from the primary tumor for evaluation. A blinded central review board evaluated the pathological response independently of the local pathologists.

The rate of breast-conserving surgery was defined by the proportion of patients who underwent conserving surgery in relation to the eligible patients. RFS was defined as the time from randomization to the diagnosis of relapse, progressive disease, or death from any cause, and was censored at the date on which relapse-free status was verified. Secondary tumor was not treated as an event of RFS. OS was defined as the time from randomization to death from any cause, and was censored at the final follow-up date.

Toxicity was evaluated according to National Cancer Institute Common Toxicity Criteria (version 2).

Study Treatment

Chemotherapy

Four courses of doxorubicin $60 \text{ mg}/\text{m}^2$ and cyclophosphamide $600 \text{ mg}/\text{m}^2$ (AC) administered intravenously on day 1 every 3 weeks were followed by 12 courses of weekly paclitaxel $80 \text{ mg}/\text{m}^2$, prior to radiation therapy and surgery. Although the method of premedication was left to the judgment of each investigator, administration of 5-HT₃ antagonist and dexamethasone was strongly recommended on the AC regimen. Dexamethasone was given before weekly paclitaxel.

Dose Modification. AC could be postponed for a maximum of 16 days if the ANC was $<1,500/\text{mm}^3$ or the platelet count was $<75,000/\text{mm}^3$. If any nonhematological toxicity except for alopecia did not recover to grade 1 during this period, the protocol treatment had to be discontinued.

Paclitaxel could be postponed for a maximum of 16 days if the ANC was $<1,000/\text{mm}^3$ or the platelet count was $<75,000/\text{mm}^3$. If any nonhematological toxicity except for alopecia, neuropathy (motor, sensory), edema, arthralgia, and myalgia did not recover to grade 1, and if alopecia, neuropathy (motor, sensory), edema, arthralgia, and myalgia did not recover to within grade 2 during this period, the protocol treatment had to be discontinued.

Radiation Therapy

Patients received radiation therapy after the completion of chemotherapy. Radiation therapy with a dose of 45 Gy in 25 fractions over 5 weeks using tangential fields to the whole breast followed by a 10-Gy boost in 5 fractions over 1 week to the original tumor region was delivered.

Surgery

Twelve to 16 weeks after the completion of sequential chemoradiation therapy, patients underwent appropriate surgery according to the size and position of the primary tumor. The surgical margin in lumpectomy specimens had to be free of invasive or noninvasive breast cancer; otherwise a repeat excision had to be performed. Sentinel lymph node biopsy was allowed for clinical N(-) patients before chemoradiation therapy.

Hormone Receptor and HER2 Overexpression

Estrogen receptor (ER) status and progesterone receptor (PgR) status were determined by immunohistochemistry at each institute. Tumors with >10% positively stained tumor cells were classified as positive for ER and PgR. HER2 status was also determined at each institute by immunohistochemistry or by fluorescence in situ hybridization (FISH) analysis. HER2-positive tumors were defined as 3+ on immunohistochemistry staining or as positive by FISH.

Study Design and Statistical Methods

This trial was designed to evaluate safety and efficacy in terms of the pCR rate of preoperative sequential chemoradiation therapy. In this study, the sample size was determined to be 104 patients, considering: (1) providing at least 90% power with a one-sided alpha of 0.05 based on an expected pCR rate of 50% and a threshold of 35%, and (2) having the 95% CI of the estimated pCR rate within $\pm 10\%$ around 50% for sufficient precision of pCR in order to support decision-making for a next phase trial.

If the null hypothesis of the primary endpoint is rejected, a preoperative sequential chemoradiation therapy will be considered as a promising investigational new regimen in a proceeding phase III trial which compares nonsurgery to surgery after preoperative chemoradiation therapy.

Statistical analyses were performed with SAS release 9.1 (SAS Institute, Cary, N.C., USA). This trial was registered UMIN-CTR (www.umin.ac.jp/ctr/) as No. C000000114.

Interim Analysis for Futility and Monitoring

In this phase II trial, an interim analysis was planned once for futility when the 7th eligible patient's pathological response was evaluated. If there was at least one pCR case, registration was continued. If the true pCR rate were as expected (50%), the probability of no pCR case among the first 7 eligible patients would be less than 1%; thus, the registration was to be discontinued for futility. The JCOG Data and Safety Monitoring Committee (DSMC) independently reviews the interim analysis report and recommends that the trial either be continued or terminated early. Central monitoring is performed every 6 months by the JCOG Data Center to evaluate and improve study progress and quality.

Results

Patient Characteristics

Between June 2004 and April 2005, one hundred eight patients were prospectively enrolled from 29 institutions. As no patient was ineligible, 108 patients were assessed for safety and efficacy. First 7 successive eligible patients were analyzed to evaluate interim pathological efficacy accord-

Table 1. Patient characteristics

	Patients (n)	%
Total	108	
Age, years		
Median (range)	50 (23-69)	
Tumor size		
T1c	1	1
T2	104	96
T3	3	3
Axillary nodal status		
N0	54	50
N1	52	48
N2	2	2
Stage		
I	1	1
IIA	52	48
IIB	51	47
IIIA	4	4
IIIB	0	0
ER and PR		
Both negative	39	36
Either one positive	67	62
Unknown	2	2
HER2		
Overexpression	34	31
Negative	71	66
Unknown	3	3
Histological type		
Invasive	107	99
DCIS	1	1
Histological grade		
1	19	18
2	34	31
3	27	25
Not assessed (not IDC)	6	6
Unknown	22	20
Sentinel LN biopsy		
Performed	12	11
Not performed	96	89

DCIS = Ductal carcinoma in situ; IDC = invasive ductal carcinoma; LN = lymph node.

ing to the protocol. None of them showed a pathologically complete response, which made the DSMC recommend discontinuation of the trial. At the time of the recommendation of the DSMC, patient accrual was completed because the patient enrollment rose rapidly beyond our expectations. For the patient who had not undergone preoperative radiation therapy, the preoperative treatment was changed to the standard therapy (preoperative AC-weekly paclitaxel followed by surgery \pm postoperative radiation therapy) after the recommendation of the DSMC. Thus, 82 patients completed the protocol treatment and 9 discontinued the treatment due to aggravation of the primary tumor,

while 7 and 5 terminated the treatment due to adverse events and patient refusal related to adverse events, respectively. Five patients discontinued due to a recommendation to change treatment modalities at the trial termination.

The median age of the eligible 108 patients was 50 years, and 54% of patients were premenopausal. One hundred four patients had T2 tumors (96%), with 3 patients having T3 tumors and 1 having T1 tumors (table 1). Thirteen patients had papillotubular tumors, with 19 patients having solid tubular tumors and 46 having schirras tumors. The remaining patients had other histological types.

The toxic effects in chemotherapy and radiation therapy are shown in tables 2 and 3.

Surgery

Of all of the eligible cases, 106 underwent surgery and 2 did not because of disease progression (breast conservation surgery in 96 and mastectomy in 10 including 1 patient who underwent mastectomy after breast conservation surgery because of a positive margin). The breast conservation rate was 88.9% (96/108). The breast conservation rate was 94.0% (78/83) if the analyzed patients were limited to those who completed the protocol therapy. Eight patients underwent reoperation 0–49 days after the initial surgery for reasons of positive surgical margins in 4, surgical wound dehiscence in 2, and other events in 2 patients.

Evaluation of Pathological Efficacy

Of all 106 surgical cases, 27 had pCR (complete) including 1 patient with residual tumor in the nodes, while 12 had pCR with ductal carcinoma in situ including 1 patient whose status of residual tumor in the nodes was unknown. The intention-to-treat analysis revealed that the pCR rate was 36.1% (39/108), which was lower than expected and could not reject the null hypothesis ($p = 0.44$). The pCR rate was 41.6% (37/89) if analysis was limited to patients who completed the protocol therapy. Recurrence status and the relationship between the pCR rate and hormone receptor (HR)/HER2 subtype are shown in table 4. Triple-negative breast cancer and HER2 one had a pCR rate of 52 and 57%, respectively, whereas luminal type cancer showed a pCR rate of 24%. Recurrence status including local and distant metastases differed very much from one subtype to another.

Clinical Efficacy Evaluation

Forty-six patients went into CR while 37 went into PR. The clinical complete response rate was 42.6% (46/108).

The RFS and OS are depicted in figures 1 and 2, respectively. The 4-year RFS and OS were 84.1% (95% CI 75.6–89.8) and 93.5% (95% CI 86.8–96.8), respectively.

Table 2. Treatment-related toxicities – chemotherapy

	AC (n = 108)		Weekly paclitaxel (n = 106)	
	all grades	grades 3 and 4	all grades	grades 3 and 4
Nonhematologic toxicities, n (%)				
Fatigue	55 (51)	2 (2)	52 (49)	1 (1)
Anorexia	52 (48)	3 (3)	23 (22)	1 (1)
Nausea	78 (72)	1 (1)	21 (20)	0
Mucositis/stomatitis	40 (37)	0	19 (18)	0
Vomiting	44 (41)	4 (4)	4 (4)	0
Febrile neutropenia	3 (3)	3 (3)	1 (1)	1 (1)
Neuropathy: motor	2 (2)	0	20 (19)	4 (4)
Neuropathy: sensory	3 (3)	0	83 (78)	4 (4)
Hematologic toxicities, n (%)				
Leukocytes	85 (79)	23 (21)	92 (87)	16 (15)
Hemoglobin	23 (21)	0	62 (58)	1 (1)
Platelets	1 (1)	0	0	0
Neutrophils	74 (69)	27 (25)	70 (66)	11 (11)
GPT	44 (41)	1 (1)	61 (58)	0

Table 3. Treatment-related toxicities – radiation therapy

	All grades	Grades 3 and 4
Early-phase toxicities, n (%)		
Radiation dermatitis	74 (83)	0
Radiation pneumonitis	0	0
Late-phase toxicities, n (%)		
Radiation dermatitis	54 (61)	0
Radiation pneumonitis	1 (1)	0

Eighty-nine patients who received radiation therapy as the protocol treatment were evaluated.

Table 4. Recurrence status and relationship between pCR rate and HR/HER2 subtype in all eligible 108 patients

Subtype	n	pCR, n (%)	Recurrence status		
			local, n	distant, n	total, n (%)
HR+/HER2–	46	11 (24)	2	8	10 (22)
HR+/HER2+	20	8 (40)	0	3	3 (15)
HR–/HER2–	25	13 (52)	2	4	6 (24)
HR–/HER2+	14	8 (57)	0	1	1 (7)
Unknown	2	0 (0)	0	0	0 (0)

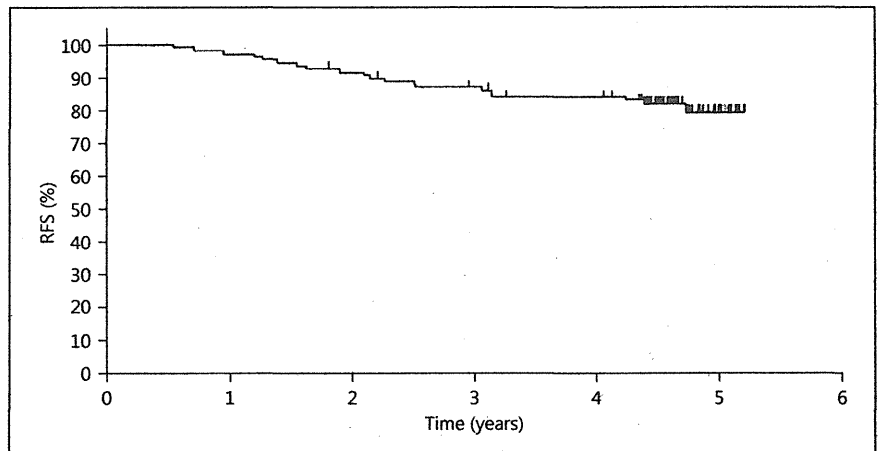


Fig. 1. RFS of the study patients.

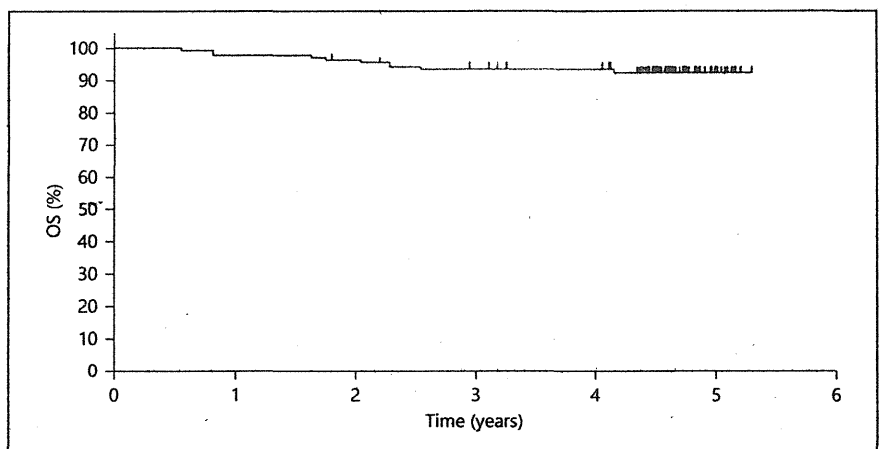


Fig. 2. OS of the study patients.

Discussion

This study was performed to evaluate the effect of chemotherapeutic regimens, which were expected to be most efficacious at the time of the start of this study, combined with radiation therapy using an index of a pCR rate. This study is significant in exploring effective systemic or local therapy.

This study showed that preoperative sequential chemoradiation therapy was effective and tolerable. Green et al. [10] reported a pCR rate of 30% in their study, where their chemotherapeutic regimen as well as their definition of a pCR rate was comparable to ours. Our pCR rate of 36.1% exceeded theirs by 10% or less in the local irradiated sites, which seem to explain our results.

On the other hand, pCR rates differed greatly between breast cancer subtypes. The triple-negative subtype as well as the HER2 subtype had a pCR rate higher than 50%,

whereas the luminal subtype showed a pCR rate of 24%. More interestingly, recurrence rates differed very much from one subtype to another. These results revealed that the accuracy of prognosis estimation based on the pCR rate differed among subtypes although the pCR rate was assumed to be a surrogate marker of long-term survival. This is consistent with the results of a retrospective German study [11].

We did not achieve a pCR rate as expected in this study. To realize nonsurgical treatment in the future, it may be necessary to limit patients to those of a subgroup that is efficaciously treated with preoperative sequential chemoradiation therapy at least. The results of this study suggest that patients with HER2 subtype breast cancer may be candidates for such subgroups. Since this study was done before data of trastuzumab use in the adjuvant setting was published, the agent was not prescribed to patients with HER2-positive tumors in this trial. Many papers demonstrating the efficacy of preoperative use of an-

ti-HER2 agents, including trastuzumab, have been published [12, 13]. We are interested in a future study in which an anti-HER2 agent is added to preoperative sequential chemoradiation therapy in HER2-positive breast cancer. Especially, pCR of dual HER2 blockade therapy performed in the trial of Neosphere and NeoALLTO reached 50–60% [14, 15]; therefore, a dual HER2 blockade strategy will develop the possibility of nonsurgical treatment in the near future.

In conclusion, the expected percentage of pCR was not achieved even though preoperative sequential chemoradiation therapy did not increase the risk of operative complications and could achieve a high success rate of breast-conserving surgery.

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Disclosure Statement

The authors declare that they have no competing interests.

Importance of confirming HER2 overexpression of recurrence lesion in breast cancer patients

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Abstract

Background The systemic management of metastatic breast cancer (MBC) is usually based on ER or HER2 status of the primary tumor. However, the hormonal status or the overexpression of human epidermal growth factor 2 (HER2) may change in every metastatic site because of the effects of the long-term treatment of metastatic cancer with endocrine therapy, chemotherapy, or biological agents. The purpose of this study was to investigate the frequency of change in HER2 expression in primary and distant metastatic tumors in breast cancer patients. Another objective of the study was to examine the effect of the clinical therapy on the basis of HER2 expression in a metastatic tumor.

Materials and methods In our hospital between 1991 to December 2010, retrospectively, 156 patients had biopsy or surgical resection of their metastatic site. All sample were analyzed pathologically to confirm metastatic disease and, second, to evaluate HER2 status by immunohistochemistry or by FISH.

Results The recurrence lesions were resected from the breast or lymph node ($n = 67$, local lesion), brain ($n = 27$), lung ($n = 16$), liver ($n = 20$), bone ($n = 16$), and from the stomach, intestine, ovary, and uterus ($n = 10$).

Loss, increase, or no change in HER2 overexpression was observed in 3, 5, and 92%, respectively. Positive changes of HER2 in metastatic sites were 3 (4%) local lesion, 3 (11%) brain, 1 (7%) lung, 0 (0%) liver, 2 (17%) bone, and 0 (0%) others. In 3 of these 8 patients, trastuzumab was administered. In 2 of 3 patients, trastuzumab achieved long stable disease. The negative conversion rate of HER2 expression in metastatic lesions was 37% in patients treated with trastuzumab and 6% in those not treated with trastuzumab, a significant difference between the two groups ($P < 0.05$).

Conclusions The results of this study emphasize the significance of confirming HER2 expression in a recurrence lesion. For patients with positive conversion of HER2 status, more treatment options may be available. On the other hand, the rate of loss of HER2 expression was high in patients treated with trastuzumab, suggesting that the results of biopsy may provide an opportunity to reconsider treatment strategies for these patients.

Keywords Metastatic breast cancer · HER2

Introduction

The prognosis of HER2-positive breast cancer patients has been dramatically improved by the remarkable progress in human epidermal growth factor (HER2)-targeted therapy [1]. The systemic management of metastatic breast cancer (MBC) patients is usually based on the ER or HER2 status of the primary tumor [2]. Therefore, identification of the primary tumor and whether it is HER2-positive are extremely important, and the optimum performance of the HER2 test has become a concern [3, 4]. Recent studies on breast cancer patients have indicated that the receptors of

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the metastatic lesions may differ from the heterogeneous characteristics of those of the carcinoma [5, 6]. Previous studies have shown that confirmatory biopsy of metastatic cancer is important [7, 8]. However, the biopsy of the metastatic lesion is accompanied by surgical stress. Therefore, confirmation of HER2 expression in all distant metastatic lesions is a matter of debate. The effect of treatment on distant metastatic lesions, considering the lesions to be due to HER2 overexpression, is unknown. Therefore, it is necessary that we can predict there is a high possibility of a change of HER2 expression.

The purpose of this study was to investigate the frequency of change in HER2 expression in primary and distant metastatic tumors in breast cancer patients. Another objective of this study was to examine the effect of the clinical therapy based on HER2 expression in a metastatic tumor.

Materials and methods

In our hospital between 1991 to December 2010, retrospectively, 156 patients had biopsy or surgical resection of their metastatic site. All patients were identified at the time of suspected clinical or radiological recurrence by their primary oncologist. In patients with liver and lung tumors, in particular, biopsy was indicated in the presence of an isolated tumor, and differential diagnosis between primary tumor and a metastasis from breast cancer seemed to be difficult. Biopsy was also performed for patients who received treatment for a single liver or lung metastatic lesion for at least a year and were in an advanced clinical stage. Surgical resection of brain metastases was performed as palliative therapy for patients with limited brain metastases who were in a stable general condition. Biopsy of the regional lymph node metastases was performed as much as possible to confirm the status of the biological markers. Biopsy samples were fixed in formalin and embedded in paraffin before analysis. All samples were analyzed pathologically to confirm metastatic disease and, second, to evaluate HER2 status by immunohistochemistry or by FISH. Assessment of HER2 for the metastatic tissue was compared with that for the primary tumor. The pathologist analyzing the samples was unaware of the patients' original HER2 status.

Immunohistochemistry

All tissue samples were fixed in buffered 10% formalin and paraffin-embedded. For immunohistochemistry, all paraffin-embedded specimens were cut at 4–5 μm , by use of conventional histological techniques, and transferred to slides. Immunohistochemical staining was performed

automatically with the Ventanas Benchmark[®] XT, using the Her-2/neuTest 4B5 (Ventana Medical Systems, Roche, Tokyo, Japan). HER2 overexpression was scored as weak (incomplete membrane staining in any proportion of tumor cells), 2+ (complete membrane staining that is either nonuniform or weak in intensity but with obvious circumferential distribution in at least 10% of tumor cells, or invasive tumors with intense, complete membrane staining of 30% or fewer tumor cells), or 3+ (uniform, intense membrane staining of >30% of invasive tumor cells) in accordance with the guidelines of the American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) [9]. All IHC 2+ tumors were further analyzed with fluorescence in-situ hybridization to determine the HER2 gene copy level.

Fluorescence in-situ hybridization (FISH)

FISH analysis of the HER-2/neu gene was performed using the Histra HER2 FISH Kit (Jokoh, Tokyo, Japan). At least 60 tumor cells in each lesion and control cells were randomly evaluated for nuclear HER-2/neu amplification. Tumors were scored as amplified when the HER-2/neu gene-to-chromosome 17 ratio was ≥ 2.2 and cells had at least a median value of four HER-2/neu gene signals. The reliability of tissue microarray-based FISH for evaluation of the HER-2/neu oncogene in breast carcinoma has recently been confirmed in a validation study.

Statistical analysis

For statistical analysis, negative (score 0, 1, and 2 lacking amplification cases) and positive (score 2+ with HER2 amplification and score 3+ cases) groups were created. For correlation of data between primary tumors and metastases, the Wilcoxon signed ranks test was applied using the "Superior Performing Software System" (SPSS for Windows, Microsoft Japan). *P* values of <0.05 were considered statistically significant.

Results

Metastatic tumors were examined from the breast or lymph node ($n = 67$, local lesion), brain ($n = 27$), lung ($n = 16$), liver ($n = 20$), bone ($n = 16$), and from the stomach, intestine, ovary, and uterus ($n = 10$) (Table 1). Disease-free interval for the patients is shown in Table 1. The median duration between diagnosis of the primary tumor and identification of the metastatic lesion was 1447 days (3.88 years). In many of these cases, distinction between the metastatic lesion and primary cancer was difficult. Therefore, operation or biopsy of the lesion was performed,

which enabled the pathologist to confirm the lesions as metastasis lesions from breast cancer.

Table 2 shows the characteristics of patients with different ER or HER2 status of the primary breast cancer (PBC).

We classified the study population into 4 breast cancer subtypes (Table 2): ER(+)HER2(-), ER(+)HER2(+), ER(-)HER2(+), and ER(-)HER2(-). These subtypes were observed in 46, 10, 15, and 28% of the subject population, respectively. Patients with ER(-)HER2(+) subtype of primary breast cancer were more likely to be susceptible to brain metastasis.

Table 3 shows the modulation of HER2 in primary breast cancer specimens and in metastatic breast cancer specimens. Positive changes of HER2 in metastatic site were 3 (4%) local lesion, 3 (11%) brain, 1 (11%) lung, 0 (0%) liver, 1 (6%) bone, and 0 (0%) others. Negative changes of HER2 in metastatic site were 2 (3%) local lesion, 2 (10%) liver, 1 (10%) others and 0 (0%) brain, lung, and bone. The concordance rate of HER2 between PBC and MBC was 92% total. An increase in the HER2 expression was more frequent in the metastatic lesions of the brain than in the metastatic lesions of other organs.

Table 4 shows the correlation of the loss of HER2 expression with trastuzumab therapy in patients with HER2-positive primary breast cancer.

Forty-two HER2-positive breast cancer patients had recurrence in a variety of organs. Eight of these patients were administered trastuzumab after recurrence. In 3 of

these 8 patients, loss of HER2 expression in the metastatic lesion was confirmed. Trastuzumab as adjuvant therapy was not administered in the remaining 34 patients. In these patients, the HER2 expression was confirmed in the metastatic site. In 2 of these 34 patients, loss of HER2 expression in the metastatic lesion was confirmed. Loss of HER2 expression in the metastatic site was significantly high in the patients treated with trastuzumab ($p = 0.013$).

Table 5 shows the therapeutic effect after surgery of the metastatic site for HER2-positive breast cancer patients receiving trastuzumab.

For these patients the metastatic lesions became resistant to trastuzumab. However, immunohistochemistry (IHC) and fluorescence in-situ hybridization (FISH) of the metastatic specimens showed HER2 expression in 5 of the 8 patients. In one of the remaining 3 patients, even though HER2 expression loss was confirmed, trastuzumab was still effective. Moreover, 4 of the 5 patients were administered lapatinib, which was effective in 3 of them. Table 6 shows the response to trastuzumab therapy for patients with an increase in the HER2 expression in the metastatic lesion.

Discussion

The results of this study emphasize the significance of confirming HER2 expression in a metastatic lesion. Moreover, this study indicates that recurrent breast cancer should be treated on the basis of HER2 expression in the recurrence lesion.

First, in some patients, the change in HER2 expression in the metastatic lesion may be attributed to the HER2-targeted therapy. Several studies have shown an increase in the HER2 overexpression in metastatic lesions [10, 11]. Fabi reported that a greater difference in the HER2 overexpression in progressive disease was observed for hormone receptor (HR)-positive cases of primary breast cancer than for HR-negative PBC [12]. However, our study indicated there was no significant difference in the effect of tamoxifen use in these cases. In our study, an increase in

Table 1 Patients' characteristics 1

Recurrence site	Number (%)	DFI (days)
Local (breast, Ax-LN)	67 (42.9)	1475 (89–4871)
Brain	27 (17.3)	931 (99–3821)
Lung	16 (10.3)	1907 (643–4565)
Liver	20 (12.8)	1279 (87–3200)
Bone	16 (10.3)	1757 (204–6537)
Others (intestine/ovary)	10 (6.4)	1518 (321–2100)
Total	156 (100)	1447 (87–4871)

Ax-LN axillary lymph node, DFI disease-free interval

Table 2 Patients' characteristics 2

ER estrogen receptor; HER2 human epidermal growth factor 2

Recurrence operation site	Total no.	Primary breast cancer							
		ER(+)HER2(-)	ER(+)HER2(+)	ER(-)HER2(+)	ER(-)HER2(-)				
Local	67	35	52%	8	12%	9	13%	15	23%
Brain	27	5	18%	3	11%	9	33%	10	37%
Lung	16	6	37%	2	13%	1	6%	7	44%
Liver	20	9	45%	3	15%	2	10%	6	30%
Bone	16	9	56%	1	6%	3	19%	3	19%
Others	10	6	60%	1	10%	0	0%	3	30%
Total	156	70	45%	18	11%	24	15%	44	28%

Table 3 Modulation of HER2 in PBC and in MBC

Recurrence operation site	Total no.	HER2							
		Negative to negative		Positive to positive		Negative to positive		Positive to negative	
Local	67	47	70%	15	22%	3	4%	2	3%
Brain	27	12	18%	12	18%	3	11%	0	0%
Lung	16	12	75%	3	19%	1	6%	0	0%
Liver	20	15	75%	3	15%	0	0%	2	10%
Bone	16	11	69%	4	25%	1	6%	0	0%
Others	10	9	90%	0	0%	0	0%	1	10%
Total	156	106	68%	37	24%	8	5%	5	3%

PBC primary breast cancer, MBC metastatic breast cancer, HER2 human epidermal growth factor 2

Table 4 Correlation of the loss of HER2 expression with trastuzumab therapy in patients with HER2-positive primary breast cancer

Received trastuzumab with HER2 positive	HER2 status in MBC				Total
	Positive to positive		Positive to negative		
Yes	5	63%	3	37%	8
No	32	94%	2	6%	34
Total	37	88%	5	12%	42

P value = 0.013

ER estrogen receptor, PR progesterone receptor, HER2 human epidermal growth factor 2

HER2 overexpression was recognized in 8 (5%) patients. In 5 of the 8 patients, trastuzumab was not administered. Unfortunately, because positive conversion of HER2 expression status in the metastatic lesions of these 5 patients was identified in this retrospective study, trastuzumab had not been used in their treatment, and therefore the potential effects of this drug remained unknown. However, in 2 of the 3 patients, trastuzumab achieved long stable disease. Our data suggest that the presence or absence of HER2 expression in the metastatic lesion in HER2-negative PBC could be confirmed by molecular target therapy. However, the effect of trastuzumab on liver and lung metastasis in 1 patient was different. Therefore, in a patient with several metastasis lesions, selection of the ideal organs for confirming the HER2 status of the tumor is complicated.

Second, an alternative therapy may be administered to a patient whose metastatic lesion shows loss of HER2 expression. Our study showed that the rate of loss of HER2 expression in the metastatic lesion is higher in the group administered trastuzumab than that in the untreated group ($p = 0.05$). Therefore, loss of HER2 expression in the metastatic lesion may be attributed to trastuzumab therapy. However, there were no significant differences in the periods of trastuzumab use and loss of HER2 expression in the metastatic lesion. Therefore, 3 of these patients stopped

receiving trastuzumab therapy and continued to receive only chemotherapy. However, one of the 3 patients resumed trastuzumab and chemotherapy because the levels of the tumor markers (carcinoembryonic antigen, serum HER2) were elevated. Another reason for resumption of trastuzumab administration for this patient was that the results of needle biopsy might not reflect the expression status of HER2 throughout the metastatic lesion because of the large size of the lesion.

Third, when HER2 expression was reconfirmed in a recurrent lesion of a patient who was resistant to the agent of molecular treated therapy, an alternative molecular target reagent was recommended. In our study, trastuzumab was substituted with lapatinib for 5 patients. The conditions of 4 of the 5 patients improved after treatment with lapatinib. Lapatinib is an oral dual tyrosine kinase inhibitor that selectively inhibits the epidermal growth factor receptor (EGFR/ErbB1) and HER2/ErbB2. Clinical data have shown that for patients with HER2-positive breast cancer, lapatinib is effective as a monotherapy or in combination with trastuzumab, and in trastuzumab-resistant patients [13]. However, withdrawal of trastuzumab or chemotherapy can be clinically challenging. Confirmation of HER2 overexpression in the metastatic lesion may enable easy selection of one therapy and withdrawal of other therapy.

Finally, it is important to reexamine the HER2 expression status in the primary tumor before examining the metastatic lesion, because the accuracy of examination of HER2 overexpression remains a problem. If the HER2 expression status in the primary tumor is negative, biopsy of the metastatic lesion should be considered.

HER2 immunohistochemistry or HER2 FISH assays are imperfect and are less than 100% accurate and reproducible. ASCO-CAP recommends that the HER2 test must be high quality and reproducible. Our laboratory has performed this study according to a diagnosis protocol recommended in ASCO-CAP guidelines [9]. The HER2 test performed in this study shows 95% concordance with another validated test in the positive and negative assay values. In this study, we

Table 5 Therapeutic effect after surgery of the metastatic site for HER2-positive breast cancer patients receiving trastuzumab

Case no.	Metastatic site	Clinical response	Biopsy site	HER2 change	Post-treatment	Clinical response
1	Liver	PD	Liver	Negative	Trastuzumab with paclitaxel	SD
2	Bone	PD	Duodenum	Negative	None	PD
3	Soft tissue	PD	Soft tissue	Negative	None	SD
4	Breast	PD	Breast	No change	Lapatinib with capecitabin	PR
5	Bone	PD	Bone	No change	Lapatinib with capecitabin	SD
6	Bone	PD	Brain	No change	Lapatinib with capecitabin	PD
7	Liver	CR	Brain	No change	Trastuzumab	SD
8	Lung	PR	Brain	No change	Lapatinib with capecitabin	PR

Duration with trastuzumab: HER2-negative change versus no change: 24 versus 43 months

SD stable disease, PD disease progression, PR partial, CR complete

Table 6 Response to trastuzumab therapy for patients with an increase in HER2 expression in the metastatic lesion

Case no.	Biopsy site	Primary subtype	DFI	Post-treatment	Another metastatic sites	Clinical response
1	Lung	ER(-)HER2(-)	72 M	Trastuzumab with Paclitaxel	Lung	Long SD
2	Sc LN	ER(+)HER2(-)	56 M	Trastuzumab with Paclitaxel	Liver/lung	PD/long SD
3	Inflammatory breast	ER(+)HER2(-)	15 M	Trastuzumab with Paclitaxel	Liver	PD

DFI disease free interval, HER2 human epidermal growth factor 2, M month, long SD long stable disease, PD disease progression, Sc LN supraclavicular lymph node

performed the HER2 test with HER2-positive and HER2-negative specimens. In addition, HER2 analysis of discordant cases by IHC was performed with FISH. Unfortunately, all HER2 tests were performed with FISH. This study is not a randomized study. However, this study demonstrated 8% discordance in HER2 status. Several studies have shown discordance between HER2 status between the primary tumor and metastases in 7–26% of cases [10, 11, 13]. In this study, the prevalence of HER2 discordance was similar if not higher than that mentioned in previous reports. Simmons demonstrated that patients were motivated to undergo biopsy to confirm their metastases, and even when the biopsy did not affect management, they reported reassurance in having tissue confirmation of their disease [11]. The purposes of treatment for metastatic breast cancer are extension of survival and improvement of quality of life. However, because of surgical stress, confirmation of HER2 expression in a recurrent lesion is impossible for many patients. In this study, the median hospital stay (range) after biopsy was: 0 (0–7 days) days for breast and regional lymph node recurrences, 1 (0–16) for liver metastases, 8 (0–22) for lung metastases, 2 (0–30) for bone metastases, and 17 (3–72) for brain metastases. A good indication for biopsy intended to examine biomarkers may be metastatic sites with minimum invasion and early resumption of treatment. In addition, some metastatic sites are resected as palliative therapy for patients with brain metastases. After the surgery, the ER

and HER2 status in the resected metastatic sites should be examined. In this study, no differences were observed in the changes of the biological markers among metastatic sites. It may be important to select appropriate candidates for biopsy in future studies with a prospective design.

Our study shows that molecular target agents achieved a partial response in patients who had an increase of HER-2 expression in the metastatic lesion. Before confirming the HER2 expression in a recurrent lesion, it is important to judge the indication of biopsy by considering the rate of increase in the HER2 expression and the effect of therapy. However, because of the small number of cases included in this study it is not possible to come to any definitive conclusions regarding confirmation of HER2 expression in a recurrent lesion. Further prospective studies of larger numbers of patients are required to clarify the results in greater detail. The discordances observed in HER-2 expression between primary tumor and a recurrent lesion were 8%. An increase in HER2 overexpression was recognized in 5% of patients. Use of trastuzumab or lapatinib was effective against HER2-overexpressing metastatic tumors. In this study, patients treated with trastuzumab had a tendency to lose HER2 overexpression in metastatic lesions, suggesting that biopsy of metastatic lesions may enable suitable changes in treatment strategies.

Conflict of interest None declared.