nodes was equal. The identification rate via fluorescence or blue dye was defined by the proportion of patients with SLNs identified with either method. Exact 95 % confidence intervals were obtained on the basis of binomial distribution. Subgroup analyses of the SLN identification rate were conducted according to age and body mass index (BMI) using Fisher's exact test. Metastasis rates were separately obtained for flu^+/dye^+ SLNs, flu^+/dye^- SLNs, flu^-/dye^+ SLNs, and para-SLNs (flu^-/dye^-). They were also separately obtained for ordered flu^+ SLNs. The prevalence of adverse events was assessed. In order to use the sign test (alpha, 0.05; power, 0.90), results from 100 patients were required to detect whether the number of flu^+/dye^- SLNs was greater than that of flu^-/dye^+ SLNs in 66 % or more of eligible patients.

RESULTS

From February to October 2010, SLN biopsy was performed in 100 patients (mean age, 60 years; range, 29–75 years) with early-stage breast cancer. One patient was excluded in whom hormone therapy was administered before biopsy. Thus, 99 patients were eligible for further assessment. Of these, ductal carcinoma in situ was diagnosed in 7 %, while invasive ductal carcinoma was diagnosed in 93 %. Patient and tumor characteristics are summarized in Table 1.

Overall, the ICG fluorescence method identified an average of 3.4 SLNs in 98 of 99 patients (detection rate, 99 %). The median difference between the number of lymph nodes identified by the fluorescence and blue dye methods was one (range, 0–6 nodes), and the number of SLNs identified by the former method was significantly higher than that identified by the latter method ($p < 0.001$). Therefore, the SLN detection rate using the ICG fluorescence method was significantly higher than that by the dye method (99 vs. 78 %, $p < 0.001$; Table 2). Furthermore, SLN identification by fluorescence was independent of age and BMI (Table 3).

Table 4 summarizes the data obtained from the 99 patients ($n = 340$ SLN specimens) by the detection method. Of these patients, positive SLN identification was achieved by both methods in 78 % (77 of 99, flu^+/dye^+), ICG fluorescence alone detected SLNs in 69 % (68 of 99, flu^+/dye^-), and para-SLNs were identified in 35 % (35 of 99, flu^-/dye^-). In these 35 patients, true SLNs were identified using the ICG fluorescence and/or blue dye methods; in no patient were para-SLNs found alone. No SLNs were classified as flu^-/dye^+. Of the 340 specimens, true SLNs categorized as flu^+/dye^+ and flu^+/dye^- accounted for 36 % (121 of 340) and 47 % (160 of 340), respectively. Though para-SLNs (flu^-/dye^-) were identified in 17 % (59 of 340)

TABLE 1 Patients and tumor characteristics ($n = 99$)

Characteristic	Value
Age, years, mean (range)	60 (29–75)
Pathology	
Invasive ductal carcinoma	92 (93 %)
Noninvasive ductal carcinoma	7 (7 %)
Clinical tumor size	
Tis	4 (4 %)
T1a	4 (4 %)
T1b	15 (15 %)
T1c	39 (39 %)
T2	34 (34 %)
T3	1 (1 %)
Tx	2 (2 %)
Grade	
1	36 (36 %)
2	37 (37 %)
3	23 (23 %)
Unknown	3 (3 %)
Estrogen receptor	
Negative	17 (17 %)
Positive	81 (82 %)
Unknown	1 (1 %)
Progesterone receptor	
Negative	24 (24 %)
Positive	73 (74 %)
Unknown	2 (2 %)
HER2	
Negative	37 (37 %)
1+	32 (32 %)
2+	15 (15 %)
3+	12 (12 %)
Unknown	3 (3 %)
BMI (kg/m^2)	
<18.5	11 (11 %)
≥18.5, <22	39 (39 %)
≥22, <25	32 (32 %)
≥25 <30	13 (13 %)
≥30	4 (4 %)

BMI body mass index

TABLE 2 Comparison of sentinel lymph node detection between the ICG fluorescence method and the dye method

Characteristic	Result	*p*
Difference in number of lymph nodes identified		
Difference (ICG fluorescence–blue dye)	1.0 (range, 0–6)	<0.001
Detection rate		
ICG fluorescence	99 % (98/99)	<0.001
Dye	78 % (77/99)	

ICG indocyanine green

TABLE 3 SLN detection rate according to age and BMI using the ICG fluorescence method and the dye method

Characteristic	ICG (%)	p^a	Dye (%)	p^a
Age (years)				
<50	100 (30/30)	1.00	87 (26/30)	0.03
≥50, <60	100 (19/19)		95 (18/19)	
≥60, <70	97 (34/35)		69 (24/35)	
≥70	100 (15/15)		60 (9/15)	
BMI (kg/m^2)				
<18.5	100 (11/11)	0.61	100 (11/11)	0.20
≥18.5, <22	100 (39/39)		79 (31/39)	
≥22, <25	97 (31/32)		75 (24/32)	
≥25, <30	100 (13/13)		62 (8/13)	
≥30	100 (4/4)		75 (3/4)	

SLN sentinel lymph node, *BMI* body mass index, *ICG* indocyanine green

[a] Fisher's exact test

TABLE 4 Classification of SLN in terms of fluorescence and dye

Characteristic	Patients, % (n = 99)	SLNs identified, % (n = 340)
Flu$^+$/dye$^+$	78 (77/99)	36 (121/340)
Flu$^+$/dye$^-$	69 (68/99)	47 (160/340)
Flu$^-$/dye$^+$	0 (0/99)	0 (0/340)
Flu$^-$/dye$^-$	35 (35/99)	17 (59/340)

SLN sentinel lymph node, *flu* fluorescence

of these specimens, 100 % of the lymph nodes were ICG fluorescence-positive if para-SLNs were excluded.

Table 5 summarizes SLN and non-SLN involvement in order of SLN removal. The first SLN was defined as the proximal lymph node draining lymphatic flow from the tumor. Involvement of the first SLN was exhibited in all 20 % (20 of 99) of the patients with positive lymph nodes. Of these 20, the first isolated node was the only positive node in 12 (60 %; 9 flu$^+$/dye$^+$, 3 flu$^+$/dye$^-$). Metastases in the second or further SLNs were identified in eight patients, all of whom had a positive first SLN. In 16 of the 20 SLN-positive patients, complete ALND was performed. No axillary lymph node involvement was detected in all eight patients with the first SLN as the only positive lymph node, whereas non-SLN metastases were not detected in 4 of 8 (50 %) patients with positive second or further lymph nodes in addition to the first positive SLN. No skin necrosis or tattoo relevant to subcutaneous ICG injection was observed. No shock or other adverse reactions due to hypersensitivity were noted.

TABLE 5 SLN and non-SLN involvement in terms of the order of SLN removal

Characteristic	Patients, %
Patients with positive SLNs	20 (20/99)
Positive SLN identified by:	
ICG	100 (20/20)
Dye	70 (14/20)
First SLN positive alone	60 (12/20)
Completion of ALND	67 (8/12)
Non-SLN negative	100 (8/8)
Non-SLN positive	0 (0/8)
First SLN and second or further positive	40 (8/20)
Completion of ALND	100 (8/8)
Non-SLN negative	50 (4/8)
Non-SLN positive	50 (4/8)

SLN sentinel lymph node, *ICG* indocyanine green

DISCUSSION

This is the first prospective study to evaluate the efficacy of SLN detection using the ICG fluorescence method. The detection rate using this method was significantly higher than that using the indigo carmine or blue dye method in patients with early breast cancer. This high detection rate may be a consequence of the greater optical sensitivity of ICG compared to the color perception of the blue dye. In previous studies, the use of ICG without fluorescence imaging did not improve the SLN detection rate (73.8 %), whereas the ICG fluorescence method used in our study achieved a detection rate of 99 %, which was comparable to that reported in previous studies.[15–20]

The ICG fluorescence method uses an integrated dye coupled with an infrared camera equipped with a 765-nm wavelength emitter. Emitted near-infrared radiation activates ICG molecules and fluorescence emissions at a wavelength of 830 nm. This makes lymphatic flow and drainage of SLNs visible as fluorescence signals. Fluorescence imaging assists the surgeon in navigating the axillary basin along the subcutaneous vessels and enables orderly and sequential SLN dissection.

Obesity is associated with the development and recurrence of breast cancer.[21,22] Obesity may inhibit accurate identification of SLNs.[23,24] As the emitted fluorescence is more attenuated through fat droplets, fluorescence may decrease in proportion to increased body mass. In preliminary studies, detection of fluorescence signals deeper than 1 cm from the skin level was difficult. Abe et al.[25] reported a significant correlation between BMI and the time and depth required to reach SLNs in the axilla. In the current study, a stable SLN detection rate was observed using ICG fluorescence regardless of BMI, whereas the

detection rate using indigo carmine dye tended to decrease as BMI increased (NS). Thus, detection of SLN by ICG fluorescence is stable regardless of BMI, which may or may not reduce operative time compared to blue dye alone. The median BMI in patients included in the present study was 21.8 kg/m^2 (range, 17.6–32.4 kg/m^2). Only 4 % of patients had a BMI > 30 kg/m^2. As obesity is more prevalent in Caucasians than in Asians, the relationship between BMI and accuracy of SLN detection using ICG fluorescence requires further investigation in the former population. Skin compression techniques have been recently developed to ameliorate the attenuation of fluorescence signals. Skin compression is a simple procedure to overcome the weaknesses of the fluorescence technique in obese patients.[26]

Because lymph flow alters with age, older age may be significantly associated with false-negative SLN biopsy results. Cox et al.[23] reported that RI counts in SLNs were inversely correlated with age. In this study, the SLN detection rate using indigo carmine dye also decreased significantly with age, while the ICG fluorescence method achieved a stable and high detection rate, even in older patients.

In this study, fluorescence-positive and dye-positive (i.e., double positive) SLNs were detected in most patients (78 %). Using the ICG fluorescence method, the first SLN can be identified as the lymph node proximal to the tumor on the basis of drainage patterns and lymphatic flow. By contrast, with the RI method, identifying SLNs in order is difficult because they are detected as hot spots regardless of the anatomical lymphatic flow. In this study, all patients with SLN involvement had positive first SLNs. This means that the first SLN detected by ICG fluorescence imaging represents the exact axillary status.

The number of SLNs resected using fluorescence imaging tends to be higher than that resected using the RI method. In this study, the median number of resected SLNs was 3.4, which was greater than that (1.7–2) reported in studies using the RI method.[5–7] This disadvantage was because of the higher optical sensitivity of fluorescence imaging and the low molecular weight of ICG, which can spread further within the lymphatic basin than blue dye. However, a positive SLN is usually identified within the first 4 resected SLNs.[27] Removal of $\leq$4 nodes is acceptable for optimal accuracy of SLN biopsy.[28,29]

The avoidance of routine application of ALND in patients with positive SLNs is currently under debate in terms of breast cancer outcome. If the tumor burden on SLNs is low, locoregional recurrence can be controlled by irradiation, adjuvant chemotherapy, and hormonal therapy. The Austrian Breast and Colorectal Cancer Study Group (ABCSG Z0011) study reported outcomes of $\leq$2 SLN-positive patients in both ALND and non-ALND cohorts.[30] If axillary clearance was omitted in patients who met the ABCSG Z0011 criteria, three or more SLNs could be resected, which is compatible with the ICG fluorescence method.

In this study, ALND procedures were unnecessarily performed in 75 % (12 of 16) of the patients with positive SLNs, whereas residual axillary disease was found in the remaining 25 % (4 of 16). Of the eight patients with a positive lymph node isolated as the first SLN, none had residual axillary disease. These results suggested that SLN biopsy can safely replace axillary clearance for surgeons otherwise willing to perform further axillary treatment. However, a direct comparison between the ICG fluorescence method and the RI method is required for ensuring the efficacy of the former method. A small study (n = 30) has already reported a high SLN detection rate using the ICG fluorescence method. Use of this method decreased the false-negative rate associated with the RI method when both methods were combined.[31] A study using three tracer agents (RI, blue dye, and ICG) recently confirmed the combination of ICG and blue dye method had the highest nodal sensitivity, which avoids the need for radioisotopes.[32] A large-scale prospective study is currently ongoing to test the concordance between these methods. This study may lead to a new proposal for the optimal method of SLN detection and subsequent axillary management in patients with early-stage breast cancer.

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ORIGINAL ARTICLE

Prognostic factors for stage IV hormone receptor-positive primary metastatic breast cancer

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Abstract
Background The purpose of this work was identify potential prognostic factors for survival in patients with primary metastatic hormone receptor-positive breast cancer undergoing endocrine therapy (ET) as first-line treatment.
Methods We investigated the clinical and pathological characteristics of 69 newly diagnosed stage IV hormone receptor-positive breast cancer patients undergoing ET between 1999 and 2009, and correlated these factors with disease progression and overall survival.
Results Multivariate regression analysis revealed that progesterone receptor (PgR) positivity (hazard ratio (HR) 0.248; $p = 0.001$) and clinical benefits of first-line ET (HR 0.386; $p = 0.008$) were significant prognostic factors for survival. When first-line ET was not effective, patients for whom second-line ET was effective survived significantly longer than those for whom second-line ET was not effective (median survival time, 45.3 vs. 25.8 months; $p = 0.0411$).
Conclusions PgR positivity and clinical benefits of first-line ET were independent prognostic factors for patients with hormone receptor-positive stage IV breast cancer. Moreover, the benefits of second-line ET in patients with a tumor resistant to first-line ET suggests the existence of drug-specific resistance to ET.

Keywords Stage IV breast cancer · Second-line endocrine therapy · Prognostic factor · PgR · Clinical benefit

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Introduction

In Japan approximately 10% of breast cancer patients present with distant metastasis at the time of diagnosis. In the 1980s, median survival time (MST) was approximately 18–24 months with or without anticancer treatment [1, 2]. Recently, however, survival of these patients has been significantly improving because of the development of novel drugs and application of alternative modes of administration of previously developed drugs [3].

In patients with metastatic or recurrent breast disease, visceral disease and shorter disease-free interval have been associated with poor survival outcome [4]. With regard to the phenotype of the primary tumors, estrogen receptor (ER) and progesterone receptor (PgR) negativity, HER2 overexpression, larger initial tumor size, and number of involved lymph nodes are associated with worse survival [5, 6]. In addition, the period of endocrine therapy (ET) treatment and hormone receptor-positivity are significant prognostic factors for survival [3, 4, 6], supporting the claim that the therapeutic decision has been appropriately directed toward ER, PgR, and HER2 [6], and that more drugs should be developed in this direction.

Recently, tumor subtypes defined by their gene expression have been widely reported to be determinants of the prognosis of primary breast cancer [7–9]. Each tumor subtype has its own clinical features and clinical outcomes, and it requires a different treatment strategy. Therefore, there is also a need to recognize prognostic factors specifically associated with each tumor subtype.

Treatment guidelines described by Hortobagyi et al. [10], the National Comprehensive Cancer Network (NCCN), the European Society for Medical Oncology (ESMO), and the Japanese Breast Cancer Society (JBCS) recommend endocrine therapy (ET) as the optimum initial treatment for hormone receptor-positive metastatic breast cancer patients. However, not all patients with hormone receptor-positive breast tumors benefit from ET. Therefore, we conducted this retrospective exploratory study to identify potential prognostic factors for patients with stage IV hormone receptor-positive primary metastatic breast cancer undergoing ET.

Patients and methods

Patients

We identified 69 female patients newly diagnosed with stage IV hormone receptor-positive breast cancer who were prescribed ET as first-line systemic therapy at the National Cancer Center Hospital in Tokyo between 1999 and 2009. The follow-up period was completed in September 2010. This study protocol had been approved by the institutional review board at the National Cancer Center Hospital in Tokyo.

Methods

All patients had invasive carcinoma histologically confirmed by core needle biopsy of the primary site. In 2000–2002, ER and PgR were detected by use of the specific antibodies 1D5 (Dako, Glostrup, Denmark) and 1A6 (Ventana Medical Systems, Tucson, AZ, USA) respectively; in 2003–2004, clones ER88 and PgR88 (Kyowa Medex, Tokyo, Japan); and in 2005–2009, clones 1D5 and PgR636 (Dako) were used. Levels of hormone receptor positivity were defined as positive staining in more than 1% or more than 10% of the tumor cell nuclei. HER2 expression was measured by use of HercepTest™ (Dako) in 2000–2002 and 2005–2009, and by use of Nichirei (Tokyo, Japan) anti-HER2/neu polyclonal antibodies in 2003–2004. HER2 positivity was defined as an immunohistochemistry (IHC) score of 3+ (intense staining of the cell membrane in more than 10% of the cancer cells) or positive fluorescence in situ hybridization (FISH) HER2 amplification signals (HER2/CEP17 signal ratio of 2 with IHC score of 2+).

Medical records were retrospectively reviewed for date of first diagnosis, date of birth, sex, histology, site of metastases, date of treatment start, treatment used, response to treatment, and date of disease progression for each of those treatments. All patients included in this study had the primary tumor as a measurable lesion. Before treatment started, all the primary tumors were measured by use of calipers. Measurement of tumor markers (CEA, CA15-3, and ST439), thoracoabdominal CT scan, and bone scintigraphy were done in all cases before treatment to screen metastatic lesions. The primary tumor was evaluated at every visit at 2–4 month intervals. Tumor markers were measured at every visit if they were elevated before treatment. Other imaging tests were done using the same modality as used before treatment when tumor growth was suspected by physical examination, symptoms, or tumor marker. Tumor response was evaluated according to WHO criteria by the investigators. Patients were classified as having a clinical benefit if they had complete response (CR), partial response (PR), or stable disease (SD) for 6 months or longer. Overall survival (OS) was calculated from the date of first diagnosis of breast cancer, with death from any cause regarded as an event. Patients who were alive at last follow-up were censored at the last follow-up date.

Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) 11.0 software (SPSS, Chicago, IL, USA). All categorical data were compared by use of chi-squared tests or Fisher's exact tests. Survival curves were derived from Kaplan–Meier estimates, and the curves were compared by use of log-rank tests. Multivariate analysis with Cox proportional hazards regression models was used to identify independent prognostic factors in all patients. All tests were two-sided. Statistical significance was set at 0.05.

Results

Characteristics of the patients

Sixty-nine patients with primary metastatic breast cancer were included in this study. The median follow-up period was 30.3 months (range: 2.0–102.4). The clinical characteristics of all 69 patients are shown in Table 1. Median age at diagnosis was 53 years (range 27–86). More than two-thirds were postmenopausal at diagnosis. Over half were categorized as clinical factor T4, approximately

Table 1 Patients' characteristics

Characteristic	Number of patients	%
All patients	69	100
Age at diagnosis		
Median (range)	53 (27–86)	–
<50 years	22	32
≥50 years	47	68
Menopausal status		
Premenopause	22	32
Postmenopause	47	68
Clinical T factor (UICC sixth edition)		
T0	1	1
T1	2	3
T2	11	16
T3	16	23
T4	39	57
Clinical N factor (UICC sixth edition)		
N0	16	23
N1	31	45
N2	12	17
N3	6	9
Site of metastasis		
Liver	16	23
Lung	26	38
Bone	48	70
Brain	1	1
Skin	3	4
Lymph node	13	19
Bone and soft tissue only	31	45
Histology		
Invasive ductal carcinoma	65	94
Invasive lobular carcinoma	3	4
Others	1	1
Histological grade		
1 (well differentiated)	2	3
2 (moderately well or partially differentiated)	39	57
3 (poorly differentiated)	22	32
Unknown	5	7
ER status		
≥10% of positively stained nuclei	63	91
<10% but ≥1% of positively stained nuclei	1	1
<1% of positively stained nuclei (negative)	2	3
Uninterpretable/missing	3	4
PgR status		
≥10% of positively stained nuclei	44	64
<10% but ≥1% of positively stained nuclei	12	17
<1% of positively stained nuclei (negative)	12	17
Uninterpretable/missing	1	1
HER2 status		
Positive	8	12
Negative	60	87
Uninterpretable/missing	1	1
First-line ET		
TAM + LHRH analog	23	33
AI	40	58
TAM	6	9

UICC Union Internationale Contre le Cancer, *ER* estrogen receptor, *PgR* progesterone receptor, *HER2* human epidermal growth factor receptor 2, *TH* endocrine therapy, *TAM* tamoxifen, *LHRH* luteinizing hormone-releasing hormone, *AI* aromatase inhibitor

three-fourths were node-positive, and above 90% had invasive ductal carcinoma. All of the premenopausal women received tamoxifen (TAM) plus luteinizing hormone-releasing hormone (LHRH) analog therapy, and all of the postmenopausal women received TAM alone (until year 2000) and anastrozole (from 2001 onward) as first-line ET. The clinical benefit rate (CBR) of the first-line ET was 67% (0% CR, 29% (20/69) PR, and 38% (26/69) SD longer than 6 months).

OS and associated prognostic factors

MST was 44.5 months (95% confidence interval (CI) 34.3–54.7). The results of the univariate analysis for OS are shown in Table 2. PgR positivity was defined by staining of more than 1% of the tumor cell nuclei (MST 48.4 vs. 28.5 months; $p = 0.0036$) and clinical benefits of first-line ET (MST 49.0 vs. 29.6 months; $p = 0.0170$) were identified as significant prognostic factors (Figs. 1, 2). PgR status and CBR of first-line ET remained significant after performing multivariate analysis (Table 3).

Relationship between responsiveness to ET and survival

Among the 46 responders to first-line ET, 4 patients continued to receive first-line ET, 7 received chemotherapy, 5 received palliative care, and 34 patients received second-line ET after failure of first-line ET. Of the 34 patients receiving second-line ET, 18 patients responded, 14 did not, and the disease was not evaluated for 2. Among the 23 non-responders to first-line ET, 11 received chemotherapy, 3 received palliative care, and 9 received

Table 2 Univariate analysis of prognostic factors

	Number of patients	MST (m)	95% CI	*p* value
Age at diagnosis				
<50 years	22	45.3	39.7–50.9	
≥50 years	47	36.5	20.2–52.8	0.6363
Menopausal status				
Premenopause	22	45.3	NA	
Postmenopause	47	38.3	28.0–48.6	0.3057
Clinical T factor (UICC sixth edition)				
T0–T3	30	45.3	27.9–62.7	
T4	39	38.3	22.0–54.6	0.4818
Clinical N factor (UICC sixth edition)				
N0	16	38.3	28.3–48.3	
N1–N3	53	46.1	31.9–60.3	0.9641
Site of metastasis				
Liver				
+	16	34.8	23.3–46.3	
−	53	46.1	33.0–59.2	0.0871
Lung				
+	26	37.1	23.6–50.6	
−	43	45.3	30.9–59.7	0.2552
Bone				
+	48	38.3	23.8–52.8	
−	21	44.5	31.0–58.0	0.9119
Bone and soft tissue only				
+	31	49.0	NA	
−	38	38.2	26.6–49.8	0.1614
Estrogen receptor status				
Positive (≥10% of stained nuclei)	63	38.3	27.6–49.0	
Negative (<10% of stained nuclei)	3	NA	–	0.2511
Positive (≥1% of stained nuclei)	64	38.3	29.0–47.6	
Negative (<1% of stained nuclei)	2	NA	–	0.1142
Progesterone receptor status				
Positive (≥10% of stained nuclei)	44	46.1	31.3–60.9	
Negative (<10% of stained nuclei)	24	37.1	33.5–40.7	0.4113
Positive (≥1% of stained nuclei)	56	48.4	43.3–53.5	
Negative (<1% of stained nuclei)	12	28.5	25.3–31.7	0.0036*
HER2/neu receptor status				
Positive	8	NA.	–	
Negative	60	44.5	35.1–53.9	0.2813
Clinical benefit rate (first-line ET)				
Positive (CR + PR + ≥6 m SD)	46	49.0	26.9–71.1	
Negative (PD + <6 m SD)	23	29.6	26.3–32.9	0.017*

* $p < 0.05$

MST median survival time, *NA* not available, *UICC* Union Internationale Contre le Cancer, *HER2* human epidermal growth factor receptor 2, *ET* endocrine therapy, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease

immediate second-line ET because of the absence of visceral metastases and the patient's own desire to receive ET. Four of the 9 patients who had initial resistance to first-line ET experienced clinical benefits with second-line ET; 2 had received anastrozole and 1 had received letrozole as first-line ET and TAM as second-line ET, whereas another had received TAM plus LHRH analog as first-line ET and medroxyprogesterone (MPA) as second-line ET (Table 4). In this population, patients who benefitted from second-line ET had significantly longer OS than those who did not (MST 45.3 vs. 19.9 months; $p = 0.0002$).

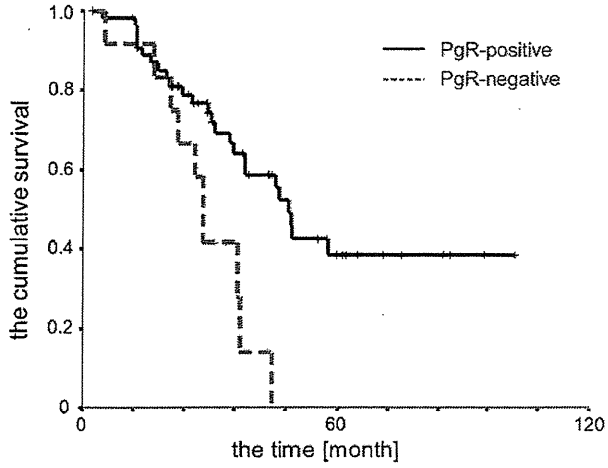

Fig. 1 Overall survival as a function of the progesterone receptor status. *Solid line*: progesterone receptor-positive patients, median 48.4 months (43.3–53.5). *Dashed line* progesterone receptor-negative patients, median 28.5 months (25.3–31.7). $p = 0.0036$

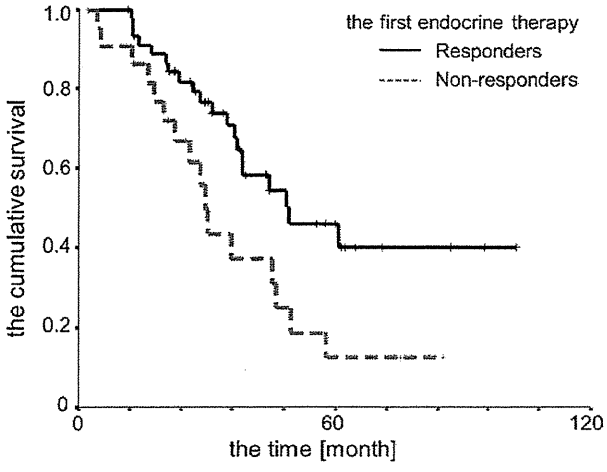

Fig. 2 Overall survival as a function of the clinical benefit rate of the first endocrine therapy. *Solid line*: responders to the first endocrine therapy, median 49.0 months (26.9–71.1). *Dashed line* non-responders to the first endocrine therapy, median 29.6 months (26.3–32.9). $p = 0.0170$

Table 3 Multivariate analysis of prognostic factors

Characteristic	HR	95% CI	*p* value
Progesterone receptor status			
Negative (<1% of stained nuclei)	3.75	1.67–8.42	0.001
Clinical benefit rate (first-line ET)			
Negative	2.63	1.32–5.24	0.006

HR hazard ratio, *CI* confidential interval, *ET* endocrine therapy

Discussion

Previous studies have shown that hormone receptor positivity is a strong prognostic marker in non-selected patients with metastatic or recurrent breast cancer [3, 5, 6, 11]. In this study, PgR positivity and clinical benefits of first-line ET were identified as independent prognostic factors for stage IV hormone receptor-positive breast cancer patients undergoing ET as the initial treatment.

Several predictors of response to second-line or subsequent ET for breast cancer—including tumor grade, ER positivity, PgR positivity, and previous ET responsiveness—have been suggested in previous studies [12–15]. Some authors have reported that 20–30% of patients with resistance to first-line ET benefit from sequential second-line ET [12, 13]. Wilson suggested that the biological characteristics of the patients and the acquired tumor changes may explain the responsiveness of some patients [12]. However, the ET options mainly used at the time of those studies (oophorectomy, hypophysectomy, androgen, estrogen, progestin, and aminoglutethimide, among others) are no longer used. Hence, those results may not be directly applicable to the current situation, in which ET consists mainly of anti-estrogens and selective aromatase inhibitors.

In this study, 4 of the 9 first-line ET-resistant patients benefitted from second-line ET, suggesting the existence of drug-specific endocrine resistance. It is important clinically to be aware of drug-specific resistance to avoid proceeding to chemotherapy rather than to second-line ET.

Several studies have suggested PgR is a strong predictor of responsiveness to TAM, indicating that ER-positive/PgR-positive tumors are strongly associated with survival benefit of patients receiving TAM treatment, in contrast with ER-positive/PgR-negative tumors [16, 17]. On the other hand, for patients undergoing letrozole treatment, PgR expression and responsiveness to treatment have a non-linear (inverted U-shape) relationship [18]. Treatment with anastrozole more effectively prevented recurrence of ER-positive/PgR-negative tumors than that of ER-positive/PgR-positive tumors [19].

Most studies have supported a role of HER2 in TAM resistance [20]. Indeed, crosstalk between ER and growth factor receptor signaling pathways has been suggested. For example, estrogen and TAM phosphorylate and activate the ER, ultimately activating growth factor-mediated signals [21, 22]. In contrast, Ellis et al. [18] reported that letrozole was more effective than TAM against ErbB-1- and/or ErbB-2-positive and ER-positive tumors. In our study, HER2 did not emerge as a prognostic marker for patients treated with first-line ET. We believe the reason is that 40 (50%) of the patients had received anastrozole as first-line ET.

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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Conflict of interest Dr Hirofumi Fujii has received Honoraria (for example lecture fees) paid by Takeda Bio and Boehringer Ingelheim.

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ORIGINAL ARTICLE

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

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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/m^2 every 3 weeks compared to 5–12% using doses ≤200 mg/m^2 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

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/m^2) every 3 weeks; the mean total dose at the onset of grade 2 neurotoxicity was 715 mg/m^2 [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/m^2 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/m^2 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).

Table 1 Patient characteristics

Variables	triPTX ($N = 188$)	wPTX ($N = 24$)	All ($N = 212$)
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

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/m^2 for patients treated with PTX every 3 weeks and 320 mg/m^2 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

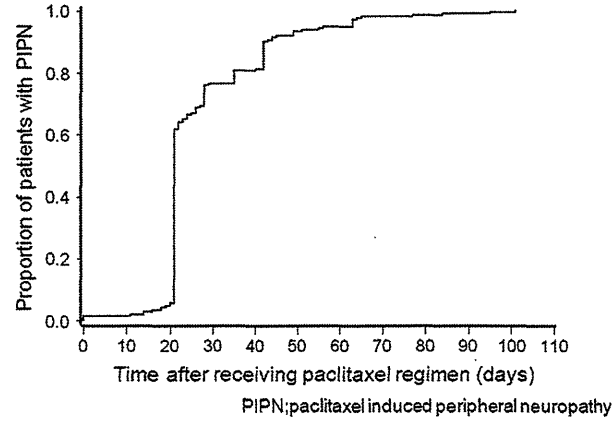

Fig. 1 Time taken for the total patient group to develop paclitaxel-induced peripheral neuropathy

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

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

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%.

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

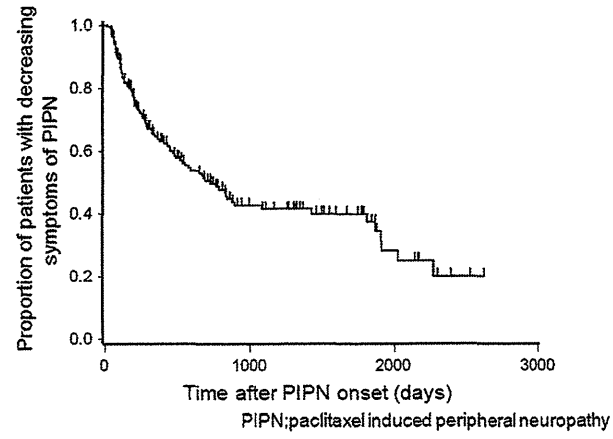

Fig. 2 Time to resolving PIPN from the time of developing paclitaxel-induced peripheral neuropathy

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/m^2 for patients treated with PTX every 3 weeks and 320 mg/m^2 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 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$\alpha 2\delta$-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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ORIGINAL ARTICLE

Locoregional recurrence risk factors in breast cancer patients with positive axillary lymph nodes and the impact of postmastectomy radiotherapy

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Abstract
Background Locoregional recurrence (LRR) after mastectomy reduces the patient's quality of life and survival. There is a consensus that postmastectomy radiotherapy (PMRT) helps establish locoregional control and reduces LRR in patients with ≥4 metastatic nodes. However, in patients with 1–3 metastatic nodes, the incidence of LRR and the role of PMRT have been the subject of substantial controversy. This study assessed the risk factors for LRR and the efficacy of PMRT in Japanese breast cancer patients with metastatic nodes.
Methods This study analyzed 789 cases of invasive breast carcinoma with metastatic nodes from 1998 to 2008. We divided the study population into 4 groups: 1–3 positive nodes with/without chemotherapy and ≥4 positive nodes with/without chemotherapy. Risk factors for LRR were identified and the relationship between LRR and PMRT was analyzed.
Results During the median follow-up of 59.6 months, 61 (7.7%) patients experienced LRR. In patients who received chemotherapy, independent LRR risk factors were high nuclear grade, severe lymphatic invasion, vascular invasion, and progesterone receptor-negative status in patients with 1–3 positive nodes, and severe lymphatic invasion and estrogen receptor-negative status in patients with ≥4 nodes. Although patients treated with PMRT had good outcomes, there was no significant difference, and PMRT did not significantly improve the outcome of the patients with all risk factors.
Conclusions With systemic therapy and adequate dissection, PMRT by itself was of limited value in establishing locoregional control. The indication for PMRT in patients with 1–3 positive nodes remains controversial.

Keywords Breast cancer · Locoregional recurrence · Postmastectomy radiotherapy · Outcome

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Introduction

For breast cancer patients and oncologists alike, locoregional recurrence (LRR) is still a clinical problem with regard to control of the disease and outcome after mastectomy. To achieve locoregional control and reduce LRR, the role of postmastectomy radiotherapy (PMRT) has been established by several randomized clinical trials (RCT) [1–4]. Based on these results, PMRT has become the standard adjuvant therapy for patients with 4 or more metastatic lymph nodes. Recently, some RCT demonstrated that PMRT improves outcome in all patients with metastatic lymph nodes, regardless of the number of positive nodes [5, 6]. However, the role of PMRT in patients with 1–3 positive nodes remains controversial [7, 8].

This study is a retrospective analysis to evaluate which clinicopathological features are predictive factors for LRR, such as the number of metastatic nodes. We also analyze the role and efficacy of PMRT in Japanese breast cancer patients.

Materials and methods

Patients and treatments

This study is a retrospective analysis of 789 patients with invasive breast carcinoma with metastatic lymph nodes

who were treated with total mastectomy and axillary lymph node dissection (level II or level III) at the National Cancer Center Hospital, Tokyo, Japan, from 1998 to 2008.

Neoadjuvant chemotherapy (NAC) was indicated for clinical stage II tumors that were larger than 3 cm in diameter, and for all stage III tumors. Adjuvant chemotherapy and/or hormone therapy were given in cases based on the most current recommendations from the St. Gallen's Consensus Meeting at the time [9–13]. Anthracycline-based chemotherapy included 4 cycles of CEF (cyclophosphamide 500 mg/m^2, epirubicin 100 mg/m^2, and fluorouracil 500 mg/m^2) every 3 weeks or 4 cycles of AC (doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2). Taxane chemotherapy included 12 cycles of weekly paclitaxel (wPTX, 80 mg/m^2). Concurrent anthracycline and taxane chemotherapy included 4 cycles of AT (doxorubicin 50 mg/m^2 and docetaxel 60 mg/m^2) every 3 weeks. Sequential anthracycline and taxane chemotherapy included 2 cycles of AT followed by 12 cycles of wPTX, AC followed by wPTX, or CEF followed by wPTX. Trastuzumab (first cycle 4 mg/kg, subsequent cycles 2 mg/kg) was added to anthracycline and taxane chemotherapy regimens in patients with overexpression of human epidermal growth factor receptor 2 (HER2).

Radiation therapy (RT) was offered to patients with 4 or more metastatic lymph nodes and/or tumors >5 cm. RT was delivered to the chest wall, including the surgical scar and regional lymph nodes (i.e., supraclavicular, infraclavicular, and axillary), by bilateral X-irradiation using the tangential technique. Because level I and II axillary dissection was performed, RT was performed in the axillary apical area (level III). The parasternal region was not included in the field. The patients were treated using a linear accelerator, and the intended dose was a median absorbed dose in the target volume of 50 Gy, given in 25 fractions over a period of 5 weeks. All patients were simulated with a conventional simulator.

Histopathological analysis

Surgical specimens were examined to determine histological subtype, histological grade (HG), nuclear grade (NG), and the presence or absence of lymphatic or vascular space invasion. Histological subtype was classified using the World Health Organization histological classification of breast tumors [14]. HG was assessed using the Scarff–Bloom–Richardson classification [15]. NG was assessed using the General Rules for Clinical and Pathological Recording of Breast Cancer, 16th Edition [16, 17]. Immunohistochemistry was used to examine tissue samples for the expression of estrogen receptor (ER), progesterone receptor (PgR), and HER2. The cutoff values for ER and PgR were 10% positive cells. HER2 status was defined based on immunohistochemical staining (IHC). The specimens that were HER2 2+ by IHC were then subjected to fluorescence in-situ hybridization (FISH). HER2-positive samples were defined as those that were HER2 3+ in IHC or HER2 2+ in IHC with an amplification ratio in FISH of $\geq$2.0. The degree of lymphatic invasion (ly) was classified by hematoxylin and eosin staining as follows: absent, no lymphatic invasion; ly1+, minimal lymphatic invasion; ly2+, moderate lymphatic invasion; and ly3+, marked lymphatic invasion. The degree of venous invasion (v) was classified as follows: absent, no venous invasion; present, venous invasion. These evaluations were performed by two qualified pathologist.

Follow-up and statistical analysis

The duration of follow-up was calculated from the first day of treatment (NAC or surgery) to the most recent medical visit on record. LRR was defined as tumor recurrence in chest wall or regional lymph nodes with or without synchronous distant metastasis.

For comparison of categorical variables, the chi-squared test was used. Locoregional recurrence-free survival (LRFS) was calculated using the Kaplan–Meier method and compared using the log-rank test. Cox's proportional hazards regression models were used to assess the prognostic significance of tumor clinicopathological characteristics on the evaluated outcomes, which were expressed as hazard ratios (HR) with 95% confidence intervals (CI). Factors that were significant at $p \leq 0.05$ in the univariate analysis were entered into the multiple regression models. All data were analyzed using SPSS software (SPSS Inc., Chicago, IL, USA).

Results

Associations between patient and tumor characteristics and LRR

The patients, divided into 2 groups based on the number of positive nodes, and their chemotherapy treatment status are shown in Table 1. All patients had 6 or more dissected lymph nodes; the median number of dissected lymph nodes was 18.6. The median number of positive nodes per patient was 3.0.

In patients with 1–3 positive nodes (n 1–3), the mean age and the proportion of postmenopausal patients were significantly higher in those who did not receive chemotherapy. The patients who received chemotherapy had tumors that were significantly higher in HG and were more likely to be ER-negative. In patients with 4 or more