Table 2 Clinical efficacy rates

	ITT ($n = 40$)		PPS ($n = 33$)	
	Palpation	MRI/CT	Palpation	MRI/CT
CR	23 (57.5 %)	24 (60.0 %)	22 (66.7 %)	22 (66.7 %)
PR	6 (15.0 %)	12 (30.0 %)	4 (12.1 %)	9 (27.3 %)
SD	1 (2.5 %)	2 (5.0 %)	0 (0.0 %)	2 (6.1 %)
PD	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)
NE	10 (25.0 %)	2 (5.0 %)	7 (21.2 %)	0 (0.0 %)
Objective response rate[a]	29 (72.5 %; 95 % CI 56.1–85.4)	36 (90.0 %; 95 % CI 76.3–97.2)	26 (78.8 %; 95 % CI 61.1–91.0)	31 (93.9 %; 95 % CI 79.8–99.3)

ITT intent-to-treat, *PPS* per-protocol set, *MRI* magnetic resonance imaging, *CT* computed tomography, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *NE* not evaluable

[a] CR + PR

Table 3 pCR rates

	ITT ($n = 40$)	PPS ($n = 33$)	Weakly ER-positive ($n = 7$)
ypT0 ypN0	14 (35.0 %)	13 (39.4 %)	1 (14.3 %)
ypT0/Tis ypN0	19 (47.5 %)	18 (54.5 %)	3 (42.9 %)
near pCR (Grade 2) ypN0	3 (7.5 %)	2 (6.1 %)	0
QpCR ypN0	22 (55.0 %)	20 (60.6 %)	0

pCR pathologic complete response, *ITT* intent-to-treat, *PPS* per-protocol set, *QpCR* quasi-pCR

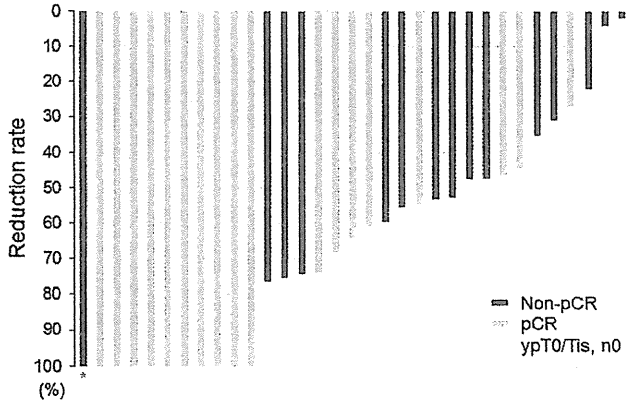

Fig. 2 Tumor response rates. Reduction in lesion size from baseline (%) to the time of mPCX therapy completion in individual patients. *This patient achieved ypT0/Tis in the breast, but an invasive tumor was found in the axillary lymph node. *pCR* pathologic complete response

Toxicity

Adverse events occurring during the study are presented in Table 4.

Grade ≥3 hematologic adverse events included leukopenia in 25 % (10/40), neutropenia in 35 % (14/40), and anemia in 5 % (2/40) of patients. Non-hematologic toxicities classified as Grade ≥3 included palmar-plantar erythrodysesthesia syndrome in 8 % (3/40) of patients, while nausea, vomiting, diarrhea, and peripheral sensory neuropathy occurred in one patient each. Interstitial pneumonia occurred in two patients (Grade 1) during mPCX therapy. No subjective symptoms were found, and the disease was only identifiable on imaging. The clinical signs of the disease resolved after observation and steroid therapy. Both patients successfully underwent postoperative FEC therapy.

One serious adverse event (pulmonary artery thrombosis) was detected after mPCX in one patient based on imaging findings. The patient had no symptoms and no reduction in oxygen saturation. A causal relationship with the study drug was ruled out based on the attending physician's judgment and the patient continued FEC chemotherapy, thereafter undergoing surgery.

Discussion

This study included women with primary TNBC or breast cancer with low ER/PgR expression, which are often associated with an unfavorable prognosis. New treatment options are necessary. To reduce the likelihood of disease recurrence and prolong the survival of patients with breast cancer, it is necessary to add other strategies to standard care. Patients with ER-positive and/or HER2-positive breast cancer may benefit from targeted therapies, such as endocrine therapy and anti-HER2 therapy. Unfortunately, there are few options for TBNC, and the currently available chemotherapies are somewhat limited. Therefore, it is essential to develop new treatment strategies for this disease. Although some novel agents are under development, we are focusing on metronomic chemotherapy based on a combination of approved anticancer drugs. The concept of metronomic chemotherapy

Table 4 Adverse events according to grade

$n = 40$	Grade 1 or 2	Grade 3 or 4
Hematologic toxicity		
Anemia (hemoglobin)	33 (83 %)	2 (5 %)
White blood cell count decreased	26 (65 %)	11 (28 %)
Neutrophil count decreased	21 (53 %)	14 (35 %)
Platelet count decreased	6 (15 %)	0
Non-hematologic toxicity		
Peripheral sensory neuropathy	30 (75 %)	1 (3 %)
Palmar-plantar erythrodysesthesia syndrome (HFS)	28 (70 %)	3 (8 %)
Nausea	28 (70 %)	1 (3 %)
Inflammation of the mucus membranes in the mouth	23 (58 %)	0
Alanine aminotransferase increased	22 (55 %)	1 (3 %)
Pyrexia	21 (53 %)	0
Nail changes[a]	20 (50 %)	0
Constipation	20 (50 %)	0
Aspartate aminotransferase increased	19 (48 %)	0
Vomiting	11 (28 %)	1 (3 %)
Diarrhea	9 (23 %)	1 (3 %)
Nail loss	7 (18 %)	0
Arthralgia	6 (15 %)	0
Myalgia	6 (15 %)	0
Eruption	4 (10 %)	0
Creatinine increased	2 (5 %)	0
Hemorrhoids	3 (8 %)	0
Blood bilirubin increased	2 (5 %)	0
Allergic reaction	2 (5 %)	0
Peripheral motor neuropathy	2 (5 %)	0
Dizziness (exertional)	2 (5 %)	0
General malaise	2 (5 %)	0
Interstitial pneumonia	2 (5 %)	0
Febrile neutropenia	0	12 (30 %)

[a] Adverse events were assessed based on the common terminology criteria for adverse events (CTCAE) version 4.0 except for "nail changes" (CTCAE version 3.0)

was based on the expectation that their anti-angiogenic effects would be associated with a reduced incidence of toxicities and avoiding drug resistance [17]. The evidence accumulated to date suggests that metronomic chemotherapy may have several new mechanisms of action, including restoration of the patient's anticancer immune response and the induction of tumor dormancy [42]. Although the results of phase III studies of metronomic chemotherapy have not yet been published, several recent studies have revealed that metronomic chemotherapy may be clinically beneficial and safe for a broad range of tumors [21–25], and this was further confirmed in a systematic literature analysis [42].

In this study, we applied the metronomic concept to PCX therapy, the first time this has been done with a combination of three drugs. The RDI for paclitaxel in the mPCX phase was almost 90 %, and the toxicities at this intensity were not serious; therefore, the combination showed good tolerability, similar to that for standard weekly paclitaxel. The metronomic PCX followed by standard FEC regimen resulted in pCR rates of 37.5 and 54.5 % in the ITT population and PPS, respectively. These values were higher than those of conventional anthracycline (A) chemotherapy (around 20 %) [5–8], taxanes (T) alone (from 5 to 12 %) [5, 28], and standard chemotherapy with a sequential combination of A and T for TNBC (around 30 %) [5]. About 5–10 % of patients with triple-negative breast cancer experience tumor progression during neoadjuvant chemotherapy because of drug resistance. Tumor progression may be found by chance because none of the subjects whose tumor progressed during neoadjuvant chemotherapy (Table 2) in this study received metronomic PCX followed by FEC.

We also analyzed the results of mPCX in breast cancer patients with weakly positive ER. Invasive breast cancer disappeared in four of these patients (ypT0/Tis) after mPCX-EFC therapy, of whom three patients were axillary lymph node negative (ypN0).

Among 35 patients who completed four cycles of mPCX, 11 achieved CR with a complete loss of lesions. Of these 11 patients, 10 had a pCR.

The positive outcomes outlined here may result from the favorable efficacy profile of metronomic mPCX itself, combined with the reduced toxicity of this dosing regimen. It is possible that a CR after the first mPCX could be a surrogate marker of pCR. Furthermore, pCR could be expected after clinical CR (cCR) in response to mPCX, while surgery in patients with cCR after mPCX could lead to pCR with good prognosis.

TNBC includes a range of phenotypes. Unfortunately, we do not yet know which subtypes, for example high or low proliferative subtypes, are the most suitable candidates for metronomic chemotherapy. However, considering the anti-angiogenic mechanism of metronomic chemotherapy, its efficacy might be independent of the tumor's proliferative capacity. To improve the pCR rate for TNBC, carboplatin and/or bevacizumab were used in combination with taxanes in two recent trials. The GeparSixto-GBG 66 and CALGB/Alliance 40603 clinical trials [43, 44] revealed that the use of carboplatin and/or bevacizumab increased the pCR rate to 50–60 %, similar to the rate for mPCX followed by FEC in our study. Regarding adverse events, carboplatin was associated mild or serious bone marrow suppression. Some patients given carboplatin required treatment with granulocyte colony-stimulating factor and some patients experienced grade 3/4 anemia and/or thrombocytopenia. By contrast, mPCX was not associated with

additional serious adverse events, which suggests it is associated with fewer toxicities and improved efficacy compared with other regimens. We are now planning to conduct translational studies focusing on a variety of biomarkers. These studies should reveal which tumor subtypes are suitable candidates for metronomic chemotherapy. We are also planning another clinical trial to confirm the usefulness of metronomic chemotherapy for TNBC.

Based on the results of Fig. 2, the tumor response during mPCX might be predictive of pCR. Almost all of the patients with cCR after mPCX achieved CpCR after FEC. This may help us to predict which patients may not require an anthracycline, thus avoiding the associated risk of cardiac toxicity. This may also help us identify which patients may not require surgery to remove the original tumor. Importantly, if a CR is achieved after mPCX therapy, the anthracycline regimen may be discontinued in patients with a pCR, which could be particularly beneficial because of the risk of cardiotoxicity associated with anthracyclines. With mPCX, we may therefore have access to a new treatment option in which potentially cardiotoxic FEC can be avoided, at least in some patients. However, if pCR is not achieved with metronomic mPCX therapy alone (without subsequent anthracycline-based chemotherapy) postoperative anthracycline-based chemotherapies may still be administered. The efficacy of postoperative chemotherapy with anthracyclines was demonstrated by Bear et al. [42], who found no differences in prognosis between patients treated preoperatively with anthracycline plus docetaxel and those treated preoperatively with anthracycline and postoperatively with docetaxel. Patients enrolled in the present study are now being followed up to determine whether pCR after four cycles of metronomic mPCX allows the avoidance of subsequent FEC chemotherapy. Notably, breast conservation surgery was possible in six patients (40 %) who were scheduled to undergo total mastectomy, while 23 (92.0 %) of patients underwent BCS as planned.

The incidence of Grade $\geq$3 non-hematologic adverse events was generally low and similar to that reported for metronomic cyclophosphamide and capecitabine [18, 44] or cyclophosphamide/methotrexate [24]. Grade $\geq$3 hematologic events occurred in 10–25 % of patients, which is somewhat higher than that reported for metronomic cyclophosphamide/methotrexate [24]. However, only one serious adverse event occurred, which was not considered related to the study drug. The rate of compliance was also high, based on the high RDI rates.

Some limitations of this study warrant mention. First, the sample size was small (only 40 patients), although it was adequately powered based on the planned sample size. Second, the pCR rate may be further improved by the combination of a PARP inhibitor or bevacizumab with metronomic mPCX [45, 46], although the benefits of adding bevacizumab would need to be balanced against the possibility of a higher incidence of grade 3 or 4 toxicities [47].

In conclusion, metronomic PCX followed by FEC chemotherapy was associated with a high pCR rate and low toxicity in patients with TNBC. Further studies of this regimen in larger numbers of patients are warranted.

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Conflict of interest Norikazu Masuda has received honoraria from Chugai. Satoshi Morita has received honoraria and research funding from Chugai. Masakazu Toi has received honoraria from Chugai and research funding from Chugai and BMS. All other authors have no conflicts of interest to declare.

Ethical standard The experiments performed in this study comply with current Japanese law.

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SPECIAL FEATURE

Breast cancer in young women: Issues and perspectives regarding patients' and survivors' care

Clinicopathological features of young patients (<35 years of age) with breast cancer in a Japanese Breast Cancer Society supported study

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Abstract
Background To clarify the clinicopathological features of breast cancer in young females, surveillance data of the Registration Committee of the Japanese Breast Cancer Society were analyzed.
Methods The clinicopathological characteristics were compared between young (<35) patients and non-young (≥35) patients among 109,617 records registered between 2004 and 2009.
Results The numbers of young and non-young patients were 2,982 (2.7 %) and 106,295 (97.0 %), respectively. The young patients had more cases of a familial history of breast cancer, more subjective symptoms, fewer bilateral tumors, lower BMIs, larger tumors, more positive lymph nodes, fewer instances of an ER-positive status, more instances of an HER2-positive status, more triple-negative tumors and more advanced TNM stages. The young patients more frequently received neoadjuvant chemotherapy and breast-conserving therapy (BCT) compared with the non-young patients. Eighty percent of all patients received adjuvant therapy. The young patients were more frequently treated with chemotherapy, molecular targeted therapy and radiation therapy than the non-young patients.
Conclusions In this study, young patients with breast cancer were diagnosed at more advanced stages and had more endocrine-unresponsive tumors than non-young patients. Further prognostic analyses should be conducted in this cohort.

Keywords Breast cancer in young females · Surveillance data

Special Feature organized by Dr. Chikako Shimizu.

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Introduction

The incidence of breast cancer in Japanese females is increasing rapidly. Approximately 61,000 females are diagnosed with breast cancer annually in Japan [1]. Breast cancer rarely occurs in very young females; however, management problems in young patients must be considered, not only health and social aspects, but also familial and reproductive problems. Breast cancer arising in younger females is reported to be more aggressive and associated with unfavorable prognoses [2–8]. Due to the limited number of patients and the lack of clinical trials using young females with breast cancer, both clinicians and patients face a lack of information regarding decision making to select treatment, including the type of surgery

and the choice of adjuvant therapy. Because subsequent life plans may be changed by what kind of treatment is chosen, information on the clinical characteristics of breast cancer in young females and trends in medical treatment is needed in clinical practice. The aim of this study was to clarify the clinicopathological features of breast cancer in young Japanese females and recent trends in treatment choices. With the support of the Registration Committee of the Japanese Breast Cancer Society (JBCS), we analyzed 109,617 cases registered between 2004 and 2009.

Materials and methods

Basic patient data

Comprehensive data on breast cancer patients diagnosed in Japan between 2004 and 2009 were registered with the Registration Committee of the JBCS. The final registry data were reported in 2010, although the patient outcome data have not yet been published. Registrations were made by 490 institutions and included 109,617 female cases. The data collected included age at diagnosis, family history, menstrual status, body mass index and clinicopathological features of the tumor, including tumor size, the presence of lymph node metastases and the receptor status (ER, PgR and HER2), the type of surgery, the use of radiation therapy and the regimens of adjuvant therapy. Since the data belong to the JBCS, permission to use the data was obtained from the JBCS.

Statistical processing

Fischer's exact test was used to compare various prevalence rates among the groups. The unpaired t test was employed to make intergroup comparisons in the numbers of cases and mean values. The significance level was set at less than 0.01 when multiple comparisons were required between two groups. All statistical processing was completed using the SAS software program (version 9.1.3; SAS Institute, Inc., Cary, NC).

Results

Patient backgrounds and clinicopathological characteristics

The age distribution of the patients is shown in Fig. 1. Young breast cancer patients, defined as those less than 35 years of age at diagnosis, were analyzed. The numbers of young and non-young patients were 2,982 (2.7 %) and 106,295 (97.0 %), respectively. Three hundred forty (0.3 %) patients were of unknown age. The median patient age was 58 years. The clinicopathological factors were compared between the young patients and the non-young patients (Table 1). Almost all of the young patients were premenopausal, and 64.1 % of the non-young patients were postmenopausal. The body mass indices of the young patients were lower than those of the non-young patients. According to the definition of the Japan society for the study of obesity, a BMI >25 was regarded as overweight; therefore, 10.4 % of the young patients and 22.8 % of the non-young patients were regarded as being overweight. On the other hand, 11.4 % of the young patients and 5.2 % of the non-young patients were regarded as being thin (BMI ≤18). A family history of breast cancer was found in 12.4 % of the young patients, which was higher than the 9.4 % observed in the

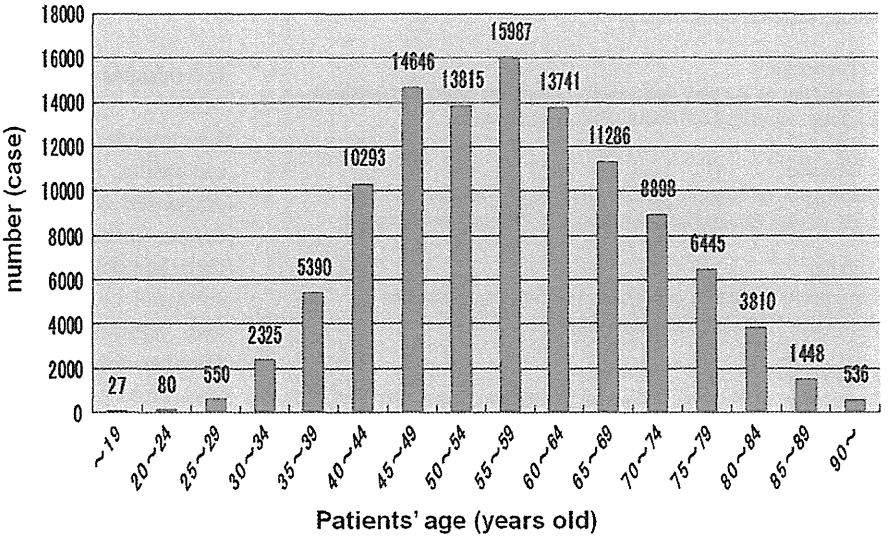

Fig. 1 Distribution of age at diagnosis among patients registered between 2004 and 2008 with the Japanese Breast Cancer Society

Table 1 Comparison of the clinicopathological factors between young and non-young patients with breast cancer

	Young patients (n = 2,982)		Non-young patients (n = 106,295)		p value
	N	(%)	N	(%)	
Menopausal status					
Pre-menopausal	2,898	97.2	35,037	33	<0.0001
Post-menopausal	48	1.6	68,107	64.1	
Unknown	36	1.2	3,151	3.0	
Body mass index (BMI)					
≦18	339	11.4	5,524	5.2	<0.0001
18< BMI ≦22	1,690	56.7	40,374	38.0	
22< BMI ≦25	514	17.2	30,842	29.0	
25<	310	10.4	24,209	22.8	
Unknown	129	4.3	5,346	5.0	
Family history of breast cancer					
No	2,399	80.4	88,195	83.0	<0.0001
Yes	370	12.4	9,967	9.4	
Unknown	213	7.1	8133	7.7	
Method of detection					
Self-detection	2,482	83.2	71,517	67.3	<0.0001
Screening (with symptoms)	107	3.6	5,233	4.9	
Screening (no symptoms)	251	8.4	22,028	20.7	
Other	99	3.3	6,352	6.0	
Unknown	43	1.4	1,165	1.1	
Bilateral breast cancer					
No	2,904	97.4	98,610	92.8	<0.0001
Synchronous	53	1.8	4,339	4.1	
Metachronous	25	0.8	3,346	3.2	
Size of tumor					
~2.0 cm	1,206	43.4	52,635	53.0	<0.0001
2.1 ~ 5.0 cm	1,231	44.3	39,976	40.2	
~5.1 cm	341	12.3	6,771	6.8	
N					
N0	2,154	72.2	83,992	79	<0.0001
N1	638	21.4	17,409	16.4	
N2	99	3.3	2,703	2.5	
N3	46	1.5	1,181	1.1	
Unknown	45	1.5	1,010	1.0	
M					
M0	2,837	95.1	102,701	96.6	<0.0001
M1	87	2.9	2,328	2.2	
Unknown	58	2	1,266	1.2	
Stage					
0	298	10	9,380	8.8	<0.0001
I	832	27.9	38,723	36.4	
II	1,172	43.9	38,185	39.8	
III	278	10.4	7,369	7.7	
IV	87	3.3	2,328	2.4	
Unknown	315	10.6	10,310	9.7	

BMI body mass index

non-young patients. Synchronous bilateral tumors and metachronous bilateral tumors were found in 1.8 % and 0.8 % of young patients, which were both lower than the rates of 4.1 % and 3.2 % observed in the non-young patients. More than 80 % of the young patients reported subjective symptoms by self detection, which was higher than the 67.3 % of non-young patients who reported similar symptoms. Asymptomatic tumors were detected on screening in only 8.4 % of the young patients, which was much lower than the rate of 20.7 % observed in the non-young patients. The young patients were more likely to be diagnosed with large tumors and advanced-stage tumors than the non-young patients. The mean tumor size was 2.9 cm in the young patients, which was larger than the 2.5 cm observed in the non-young patients ($p < 0.0001$). More than 12 % of the young patients had large tumors (>5 cm), which was higher than the rate of 6.8 % observed in the non-young patients. The distribution of histological subtypes is shown in Fig. 2. The histological tumor subtypes were classified in accordance with the classification of breast carcinoma issued by the Japanese Breast Cancer Society, which is a modified World Health Organization histological classification [9, 10]. The subtypes did not differ significantly between the young and non-young patients. Scirrhous carcinoma was the most frequent histological type in both the young and non-young patients. The frequency of solid-tubular carcinoma in the young patients tended to be higher than that observed in the non-young patients. Invasive lobular carcinoma rarely occurred in the young patients.

Biological markers

The ER, PgR and HER2 expressions were compared between the young and non-young patients (Table 2). The status of ER and PgR was determined according to the immunohistochemical (IHC) technique using monoclonal antibodies. A cutoff level of between 2 and 3 was adopted on the Allred Score [11] or 10 % as a staining proportion [12]. Tumors that were immunohistochemically scored as 3+ or 2+ with a FISH-positive status were regarded as HER2-positive in the majority of individual participating institutions. Of the young patients, 70.8 % had ER-positive tumors, which was lower than the rate of 75.0 % observed in the non-young patients ($p < 0.0001$). The HER2-positive rate in the young patients was 16.3 %, which was higher than the 14.1 % observed in the non-young patients ($p = 0.0032$). The rate of so-called 'triple-negative' [(TN), ER-, PgR- and HER2-negative] tumors was 18.3 % in the young patients, which was higher than the 13.7 % observed in the non-young patients ($p < 0.0001$).

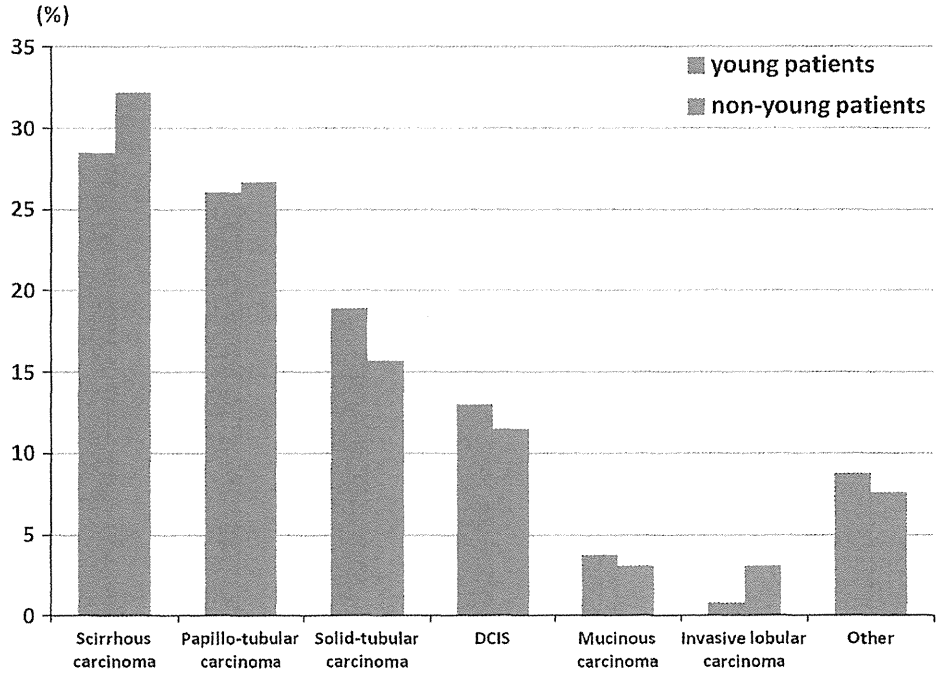

Fig. 2 Distribution of the histological subtypes of breast cancer. *DCIS* ductal carcinoma in situ

Table 2 Comparison of the hormone receptor and HER2 status between young and non-young patients with breast cancer

	Young patients (n = 2,982)		Non-young patients (n = 106,295)		p value
	N	(%)	N	(%)	
ER					
Positive	2,110	70.8	79,699	75.0	<0.0001
Negative	792	26.6	23,910	22.5	
Unknown	80	2.7	2,686	2.5	
PgR					
Positive	1,892	63.5	64,728	60.9	0.0082
Negative	999	33.5	38,539	36.3	
Unknown	91	3.1	3,028	2.9	
HER2					
Positive	486	16.3	15,010	14.1	0.0032
Negative	2,183	73.2	80,104	75.4	
Unknown	313	10.5	11,181	10.5	
Triple negative					
Yes	487	18.3	12,998	13.7	<0.0001
No	2,173	81.7	81,605	86.3	

ER estrogen receptor, *PgR* progesterone receptor, *HER2* human epidermal growth factor receptor 2

Table 3 Comparison of the type of surgery between young and non-young patients with breast cancer

	Young patients (n = 2,982)		Non-young patients (n = 106,295)		p value
	N	(%)	N	(%)	
Surgery for breast					
No	5	0.2	130	0.1	<0.0001
Breast conservation	1,844	62.7	59,822	57.0	
Mastectomy	1,030	35.1	43,982	41.9	
Other	58	2.0	1,023	1.0	
Unknown	2	0.1	49	0.1	
Axillary dissection					
No	168	5.7	7,338	7.0	<0.0001
SNB alone	1,105	37.6	40,495	38.6	
Sampling alone	63	2.1	2,912	2.8	
More than level I	1,575	53.6	53,627	51.1	
Other	14	0.5	488	0.5	
Unknown	14	0.5	146	0.1	

SNB sentinel node biopsy

Surgical treatment

The types of surgery were compared between the young and non-young patients. Both the young and non-young patients were more likely to undergo breast-conserving therapy (BCT) than mastectomy, as shown in Table 3. The rate of BCT in the young patients was higher than that observed in the non-young patients (62.7 % vs. 57.0 %), although the rate of mastectomy in the young patients was lower than that observed in the non-young patients (35.1 % vs. 41.9 %, $p < 0.0001$, respectively). Axillary lymph node dissection was performed in 53.6 % of the young patients, which was higher than the rate of 51.1 % observed in the non-young patients ($p < 0.0001$).

Adjuvant therapy

The details of the neoadjuvant and adjuvant therapy were compared between the young and non-young patients, as shown in Tables 4, 5 and 6. The rate of neoadjuvant therapy was 24.7 % in the young patients, which was significantly higher than the 11.3 % observed in the non-young patients ($p < 0.0001$). Among the patients who received neoadjuvant therapy, 97.1 % and 89.8 % of the young and non-young patients received chemotherapy, 15.7 % and 16.9 % received hormone therapy and 11.9 % and 11.0 % received trastuzumab, respectively. Anthracyclines and taxans were primarily prescribed as neoadjuvant chemotherapy in both the young and non-young patients. LHRHa was prescribed as neoadjuvant hormone therapy in 12.4 % of the young patients, and AI was prescribed in 10.6 % of the non-young patients.

Table 6 shows a comparison of the adjuvant therapies. The young patients were more likely to be treated with chemotherapy, targeted therapy and radiation therapy, but not hormone therapy, compared to the non-young patients. Among the patients who received adjuvant therapy, 55.5 % and 41.5 % of the young and non-young patients received chemotherapy, 76.2 % and 81.2 % received hormone therapy and 9.6 % and 5.8 % received trastuzumab, respectively. In contrast to that observed for neoadjuvant therapy, adjuvant therapy primarily included hormone therapy rather than chemotherapy in both the young and non-young patients. Tamoxifen and LHRHa were most prescribed as adjuvant therapy in the young patients, while AI and tamoxifen were prescribed in the non-young patients.

Table 4 Comparison of the adjuvant therapy between young and non-young patients with breast cancer

	Young patients (n = 2,982)		Non-young patients (n = 106,295)		p value
	N	(%)	N	(%)	
Neoadjuvant therapy					
No	2,211	75.2	92,992	88.6	<0.0001
Yes	725	24.7	11,912	11.3	
Unknown	3	0.1	102	0.1	
Adjuvant therapy					
No	569	19.4	19,306	18.4	0.006
Yes	2,326	79.1	84,678	80.6	
Unknown	44	1.5	1,022	1.0	

Table 5 Comparison of the neoadjuvant therapy between young and non-young patients with breast cancer

	Young patients (n = 725)		Non-young patients (n = 11,912)		p value
	N	(%)	N	(%)	
Chemotherapy	704	97.1	10,698	89.8	<0.0001
Anthracyclines	636	87.7	9,002	75.6	
Taxanes	595	82.1	8,732	73.3	
Oral FU	33	4.6	714	6.0	
CMF	1	0.1	31	0.3	
Other	4	0.6	68	0.5	
Hormone therapy	114	15.7	2,014	16.9	<0.0001
Tamoxifen	33	4.6	533	4.5	
GnRH agonist	90	12.4	256	2.1	
AI	2	0.3	1,262	10.6	
MPA	15	2.1	257	2.2	
Trastuzumab					
No	639	88.1	10,607	89.0	0.4488
Yes	86	11.9	1,305	11.0	

Oral FU oral furuorouracil (doxifluridine/tegafur-gimeracil-oteracil potassium/tegafur-uracil/capecitabine), *CMF* cyclophosphamide + methotorexate + 5-FU, *Other* irinotecan hydrochloride, gemcitabine hydrochloride, vinorelbine tartrate, *GnRH agonist* gonadotropin-releasing hormone agonist (goserelin acetate/leuprorelin acetate), *AI* aromatase inihibitors (anastrozole/exemestane/letrozole), *MPA* acetic acid medroxyprogesterone

Table 6 Comparison of the adjuvant therapy between young and non-young patients with breast cancer

	Young patients (n = 2,326)		Non-young patients (n = 84,678)		p value
	N	(%)	N	(%)	
Chemotherapy	1,290	55.5	35,163	41.5	<0.0001
Anthracyclines	1,013	43.6	24,893	29.4	
Taxanes	636	27.3	14,350	16.9	
Oral FU	162	7.0	5,262	6.2	
CMF	42	1.8	2,407	2.8	
Other	9	0.4	155	0.2	
Hormone therapy	1,772	76.2	68,712	81.2	<0.0001
Tamoxifen	1,576	67.8	28,696	33.9	
GnRH agonist	1,291	55.5	11,169	13.2	
AI	37	1.6	40,507	47.8	
MPA	7	0.3	168	0.2	
Trastuzumab					
No	2,102	90.4	79,793	94.2	<0.0001
Yes	224	9.6	4,885	5.8	
Radiation therapy					
No	872	37.5	41,257	48.7	<0.0001
Yes	1,441	62.0	43,112	50.9	
Unknown	13	0.6	309	0.4	

Oral FU oral furuorouracil (doxifluridine/tegafur-gimeracil-oteracil potassium/tegafur-uracil/capecitabine), *CMF* cyclophosphamide + methotorexate + 5-FU, *Other* irinotecan hydrochloride, gemcitabine hydrochloride, vinorelbine tartrate, *GnRH agonist* gonadotropin-releasing hormone agonist (goserelin acetate/leuprorelin acetate), *AI* aromatase inihibitors (anastrozole/exemestane/letrozole), *MPA* acetic acid medroxyprogesterone

Radiation therapy was performed in 62.0 % of the young patients, which was significantly higher than the rate of 50.9 % observed in the non-young patients ($p < 0.0001$). Radiotherapy was indicated for patients who underwent breast-conserving surgery, those with larger tumors and those with four or more positive lymph nodes at the time of surgery.

Discussion

We analyzed data obtained from a large number of breast cancer cases registered with the JBCS in order to characterize and advance our understanding of the features of young breast cancer patients. The median age of breast cancer patients was 58 years old and the percentage of young patients under 35 years of age was 2.7 % in this study. It has been established that a racial difference exists in the incidence rates and age distribution of breast cancer [13]. The age-adjusted breast cancer incidence rate for Japanese women was reported to be 73.4 per 100,000 women per year in 2007, which is still lower than the rate reported in Western countries [1]. In the US, the age-adjusted breast cancer incidence rate was 124.3 per 100,000 women per year in 2009, the median age at the diagnosis of breast cancer was 61 years of age, and the percentage of young patients under 35 years of age was 1.8 % [14]. In the 1990s, the Japanese age-adjusted breast cancer incidence rate was only 37.0–43.6 per 100,000 women per year, with the peak age at the diagnosis of breast cancer reported to range from 45–50 years of age and the percentage of young patients under 35 years of age ranged from 5–7 % [1, 15]. A rapid increase in the incidence rate was seen among middle and old age groups, especially among individuals from 45 to 64 years old; the percentage of young patients compared to all patients has shown a decreasing trend over the past 20 years [13, 15]. Early menarche, late child-bearing and a decreasing birthrate are the current trends among Japanese women, which are factors that appear to influence the present increasing rates of breast cancer in addition to changes in both foods and lifestyles from traditional Japanese customs to Western styles. As the Japanese have recently become more Westernized, the epidemiology of breast cancer might change from the previously observed patterns to Western patterns [16].

Features of the young Japanese patients' backgrounds compared to those of the non-young patients included lower BMIs, more frequent family histories of breast cancer and fewer bilateral tumors. The rate of being overweight was 10.4 % among the young patients and 22.8 % among the non-young patients. According to surveillance data of the Ministry of Health, Labor and Welfare, the rate of overweight Japanese females (BMI >25) was 20.2 % in 2007 [17]. The rates of females who are overweight between the ages of 20–29 and 30–39 are 5.9 and 11.1 %, respectively. This rate increases with age and is highest at 29.5 % among females 60–69 years of age. The weight distribution of Japanese breast cancer patients corresponds to the weight distribution of common Japanese females. In this study, young patients more frequently had a family history of breast cancer, which highlights the possibility of hereditary breast cancer accompanied by the BRCA1/2 mutation and other genetic mutations. A younger age at diagnosis is one of the features of hereditary breast cancer, as well as TN subtype and bilateral tumors [18]. In this study, since the patients were still young and had been little influenced by age, there were few metachronous bilateral tumors in the young patients. It has also been reported that a young age at diagnosis of a first cancer is a risk factor for contralateral breast cancer [19]. In our study, the biological characteristics of breast cancer in the young patients included endocrine-unresponsive tumors such as ER-negative, HER2-positive and TN tumors. Young patients tend to have larger tumors and lymph node metastasis due to delays in detection and/or rapid growth. Young patients hardly notice small-sized tumors due to fact that they have dense breasts. From a viewpoint of morphologic classification, the frequency of solid tubular carcinoma in young patients is higher, and this type has a tendency to exhibit a rapid and expansive growth pattern and prevail in patients with TN breast cancer [20]. These results are similar to those of previous studies from Western and Asian countries [2–8, 13, 21]. Breast cancer in young women is likely mainly caused by either genetic mutations or hereditary factors rather than long-term hormonal, environmental or lifestyle effects, and the biological subtypes of breast cancer in young women tend to be similar and no substantial racial differences are observed.

In terms of trends in treatment choices among young patients, the rate of BCT was higher in the young patients than in the non-young patients, in spite of the young patients exhibiting larger tumor sizes. This is due to the high rate of administration of neoadjuvant chemotherapy in young patients. In Japan, the rate of BCT was over 50 % in 2009. However, the cosmetic results of BCT were not satisfactory for all patients, and knowledge of breast reconstruction became widespread; therefore, the rate of BCT has reached a ceiling [22]. Total mastectomy and immediate reconstruction may replace BCT, especially in young patients who feel severe breast loss or who worry about intramammary recurrence. In the US, females ≤40 years of age are significantly more likely to undergo mastectomy followed by breast reconstruction than BCT compared with older females [23]. As mentioned for adjuvant therapy, both anthracyclines and taxans were used

in most of the young patients in this study. Trastuzumab was also used as adjuvant therapy. Both the pathological complete remission (pCR) rate and the survival rate of patients with breast cancer have dramatically improved because of progress in targeted therapy combined with chemotherapy during the last several years [24, 25]. A prognostic analysis of this cohort is now underway.

Preserving the ovarian function and maintaining fertility are also important issues for young patients who desire childbirth. GnRH agonists given with chemotherapy for early breast cancer have been reported to be associated with a low risk of long-term chemotherapy-induced amenorrhea and a high chance of pregnancy [26]. According to one report, of the 42 patients who attempted pregnancy, 71 % ($n = 30$) managed to achieve pregnancy, including 8 females ≥35 years of age. Although the use of GnRH agonists during chemotherapy is not yet considered to be the standard for protecting ovarian function, 12.4 % of the young patients were treated with a GnRH agonist together with neoadjuvant chemotherapy in the present study. It is important for young patients to make treatment choices based on both breast cancer subtype and personal preference with consideration for life planning, survivorship and long-term side effects. Our study has several limitations; neither the reasons for selecting the type of treatment, the timing and duration of hormone therapy, the subsequent ovarian function nor the disease prognosis was clearly elucidated in these cases. We could confirm that young patients with breast cancer are more likely to have advanced or endocrine-unresponsive tumors than non-young patients; therefore, young patients tended to be treated more aggressively with systemic therapy. Further prognostic analyses and cohort studies of long-term side effects are needed.

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Conflict of interest The authors declare that they have no conflicts of interest.

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ORIGINAL ARTICLE

Phase III randomized trial of toremifene versus tamoxifen for Japanese postmenopausal patients with early breast cancer

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Abstract
Background Toremifene, a selective estrogen receptor modulator, is used as adjuvant therapy for postmenopausal patients with breast cancer in Japan. For Japanese patients, however, only limited data are available on the efficacy and safety profile of toremifene. To establish the long term efficacy and safety of toremifene for Japanese patients, we conducted a prospective, multicenter, randomized phase III trial comparing toremifene and tamoxifen.
Patients and methods The subjects were postmenopausal Japanese patients who had undergone surgery for node-negative breast cancer. Toremifene or tamoxifen was administered for 2 years. The primary endpoint was demonstration of the non-inferiority of toremifene compared with tamoxifen in respect of 5-year survival. Secondary endpoints were cumulative overall survival, cumulative disease-free survival, effects on lipid profiles, and adverse events.
Results A total of 253 patients were enrolled. The baseline characteristics of the two treatment groups were well-balanced. Median follow-up was 66.5 months. Five-year survival was similar for toremifene and tamoxifen (97.0 vs. 96.9 %; 90 % confidence interval −3.9 to 4.1), indicating that toremifene is not inferior to tamoxifen for postmenopausal Japanese patients with early breast cancer. Cumulative overall survival and cumulative disease-free survival were also very similar for toremifene and tamoxifen (97.5 vs. 97.3 %, log-rank test $P = 0.9458$; 88.4 vs. 90.6 %, log-rank test $P = 0.3359$, respectively). Adverse events in both groups were similar and mostly mild or moderate. Thus, both are equally effective and well tolerated.

The names of institutions participating in this trial are shown in the Appendix.

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Conclusion Our results suggest that the efficacy and safety of toremifene and tamoxifen are equivalent for postmenopausal Japanese patients with early breast cancer.

Keywords Toremifene · Tamoxifen · Breast cancer · Postmenopausal · Adjuvant therapy · Dyslipidemia

Introduction

Tamoxifen is a non-steroidal anti-estrogen agent used as standard adjuvant endocrine therapy for breast cancer [1]. Tamoxifen is classified as a selective estrogen receptor modulator (SERM); the different activity of tamoxifen on each of the estrogen receptors results in a variety of tissue-specific pro and anti-estrogenic effects.

Toremifene is an anti-estrogen agent that was developed to improve upon the risk–benefit profile of tamoxifen [2]. Toremifene is also a non-steroidal anti-estrogen SERM and received approval from the Japanese government in 1995 for use in first-line treatment of postmenopausal patients with breast cancer. Toremifene and tamoxifen have similar efficacy in the treatment of advanced breast cancer [3–5], although their effects on lipid metabolism differ slightly [6–8]. However, there have been few clinical studies directly comparing the safety and efficacy of toremifene and tamoxifen in breast cancer patients. Although clinical trials conducted in Western countries show that toremifene and tamoxifen are equally effective, this has not yet been confirmed for Asian populations. In randomized trials toremifene and tamoxifen have been compared as adjuvant therapy for treatment of advanced stage breast cancer; however, no trials have been conducted on patients in the early stage of the disease. Therefore, we in the Japan Toremifene Cooperative Study Group conducted a multicenter, cooperative, randomized controlled phase III clinical trial to specifically compare the efficacy of toremifene and tamoxifen as postoperative adjuvant therapy for postmenopausal Japanese patients with early-stage breast cancer.

Patients and methods

Ethics review and patients

The study protocol was approved by the Ethics Committee/Institutional Review Board of each participating institution and was conducted in accordance with the Helsinki Declaration of 1975. Before enrollment, all patients were provided with written information about the study design and written informed consent was obtained.

The following inclusion criteria were used:

1. postmenopausal primary breast cancer;
2. ≤75 years of age;
3. tumor stage T1-2, N0, M0;
4. estrogen receptor status either positive or unknown; and
5. underwent mastectomy or breast conserving resection.

The TNM classification (1978 version) was used for staging of the breast cancer. Patients for which estrogen receptor status was unknown were included because the assay for estrogen receptors was not available in some institutions at the time of trial planning.

Randomization and treatment

Enrolled patients were randomly assigned to receive either toremifene or tamoxifen therapy. The toremifene treatment group received toremifene citrate tablets (40 mg/day) and the tamoxifen group received tamoxifen citrate tablets (20 mg/day). Medication was begun within 6 weeks of surgery and continued daily for 2 years. At the time of trial planning, the standard duration of treatment with toremifene and tamoxifen in Japan in the adjuvant setting for early breast cancer was 2 years. Patients receiving treatment for other malignancies were excluded from the study.

Assessment and statistical methods

The primary endpoint used to demonstrate the non-inferiority of toremifene compared with tamoxifen was 5-year survival. Five-year survival of Japanese patients in this trial was expected to be 90–95 %. The primary endpoint of our study was 5-year survival, thus expected survival was set at 90 %, by excluding survival-unknown cases from the total number of cases evaluated. On the basis of the Japanese phase II trial [10], toremifene and tamoxifen have similar efficacy. The number of patients for each agent, denoted by n, was estimated by use of the formula: $n = \frac{\left[z_{1-\alpha}\sqrt{2p_0(1-p_0)}+z_{1-\beta}\sqrt{p_1(1-p_1)+p_2(1-p_2)}\right]^2}{(p_1-p_2-\delta)^2}$ where z_{1-P} is the $100(1-P)$th percentile of the standard normal distribution, α is one-sided type I error of 5 %, $1-\beta$ is the power of 80 %, δ is the non-inferiority margin of 10 %, 5-year survival for both agents is 90 %, denoted by p_1 and p_2, respectively, and combined survival is given as $(p_1 + p_2)/2$. For each group, 112 cases were required to establish non-inferiority. Therefore, the number of target cases was a group of 125.

The secondary endpoints were cumulative overall survival, cumulative disease-free survival, effects on lipid profiles, and safety. Kaplan–Meier methods were used to calculate overall and disease-free survival. Efficacy was determined on the basis of the full analysis set (FAS)

population. The FAS population was all randomized patients who satisfied the major entry criteria, took at least one dose of the trial medication, and for whom data were available post randomization. Safety was assessed throughout the study by physical examination, hematology, and biochemical examination. Adverse events were assessed by using the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE, v3). For blood tests, blood samples were collected on the defined day. Time points for blood collection were before administration of adjuvant drugs, then 3, 6, 12, and 24 months after their administration. Serum lipid analysis consisted of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG). Concentrations of serum lipids were measured by standard enzymatic methods. When an enzymatic method was not used, LDL-C values were calculated by use of the equation of Friedewald et al. [9].

All patients who took at least one dose of study medication (safety population) were included in the safety analysis.

Results

Patients

Between December 1998 and November 2001, 253 patients were enrolled. Patient disposition is summarized in Fig. 1. A total of 9 violations of the patient protocol, on the basis of the selection criteria, occurred as a result of the inclusion of pre-menopausal patients (toremifene group 3, tamoxifen group 2), patients with treatment history for breast cancer (tamoxifen group 2), a patient with node-positive breast cancer (tamoxifen group 1), and a patient with ER-negative (tamoxifen group 1). As shown in Table 1, there were no significant differences in background characteristics of the patients between the two treatment groups. Five patients in the toremifene group and 3 in the tamoxifen group had histories of angina pectoris. Among eligible patients, 1 in the toremifene group and 2 in the tamoxifen group had histories of myocardial infarction. One patient in the tamoxifen group had a history of cerebral infarction. Fourteen patients in the toremifene group (11 received statins and 3 received fibrates) and 13 in the tamoxifen group (12 received statins and 1 received fibrate) were on medication for dyslipidemia. Efficacy was analyzed in the FAS population, $n = 243$ patients (123 in toremifen group, and 120 in tamoxifen group). There was no bias in the background characteristics between the two groups.

Treatment efficacy

Median follow-up was 66.5 months (range 1.6–89.7 months) at the time of data lock. Five-year survival was 97.0 % in the toremifene group (98 out of 101 cases) and 96.9 % in the tamoxifen group (95 out of 98 cases). Six patients died within 5 years after the day of registration (3 in the toremifene group, 3 in the tamoxifen group); of

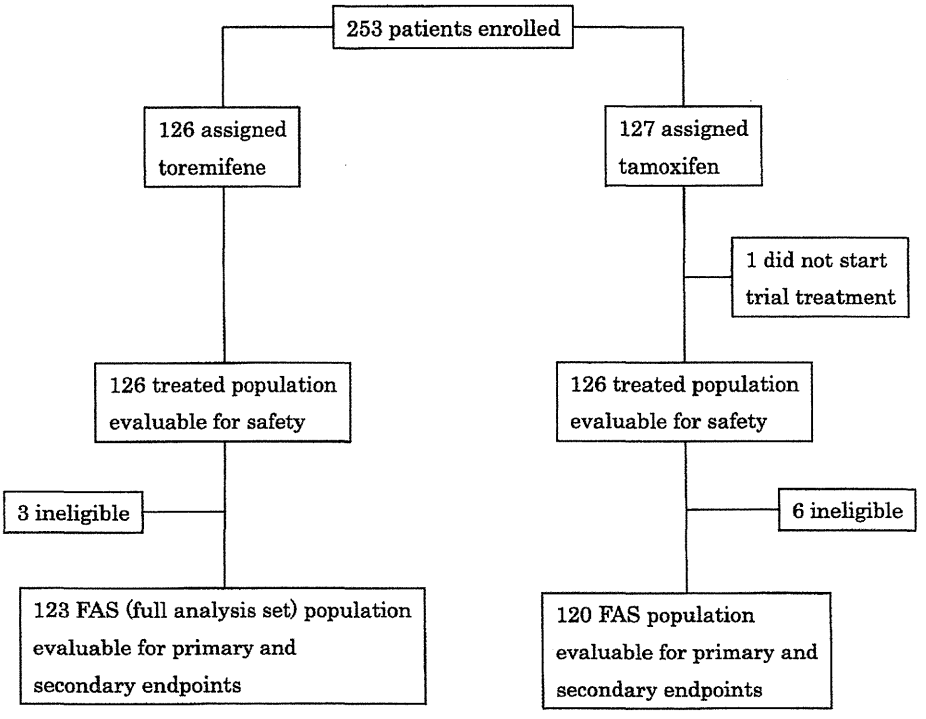

Fig. 1 Patient flow diagram

Table 1 Patient characteristics in the safety population

Variable	Toremifene ($n = 126$)	Tamoxifen ($n = 126$)	P value
Age (years)			0.172[a]
Median	64.0	62.0	
Range	49–74	47-75	
Body mass index (BMI) (kg/m^2)			0.173[a]
Median	22.5	23.6	
Range	16.9–32.1	15.8-37.2	
Performance status[b]			0.561[c]
0	124	125	
1	2	1	
Histologic subtype[b]			0.517[c]
Papilotubular carcinoma	42	40	
Solid-tubular carcinoma	30	26	
Scirrhous carcinoma	46	47	
Other	8	13	
Tumor[b]			0.709[a]
T0	2	0	
T1a	63	62	
T1b	1	0	
T2a	57	58	
Surgery[b]			0.914[c]
Mastectomy	60	63	
Breast conservation surgery	66	63	
Estrogen receptor[b]			0.356[c]
Positive	123	119	
Negative	0	1	
Unknown	3	6	

[a] Wilcoxon's rank-sum test

[b] Number of patients

[c] χ^2 test

these, 5 were due to breast cancer (2 in the toremifene group and 3 in the tamoxifen group). One death in the toremifene group was due to subarachnoid hemorrhage that was unrelated to the experimental drug. There were 33 survival-unknown cases (17 in the toremifene group and 16 in the tamoxifene group) for whom survival could not be confirmed at a point 5 years after registration. The difference in 5-year survival between the treatment groups was 0.1 %, and the 90 % confidence interval was −3.9 to 4.1; because the lower limit of the confidence interval did not exceed 10 %, these data indicate non-inferiority of toremifene compared with tamoxifen. In Fig. 2, survival curves for the toremifene arm and the tamoxifen arm are plotted by use of the Kaplan–Meier method and compared by use of the log-rank test. Six deaths were confirmed by the final

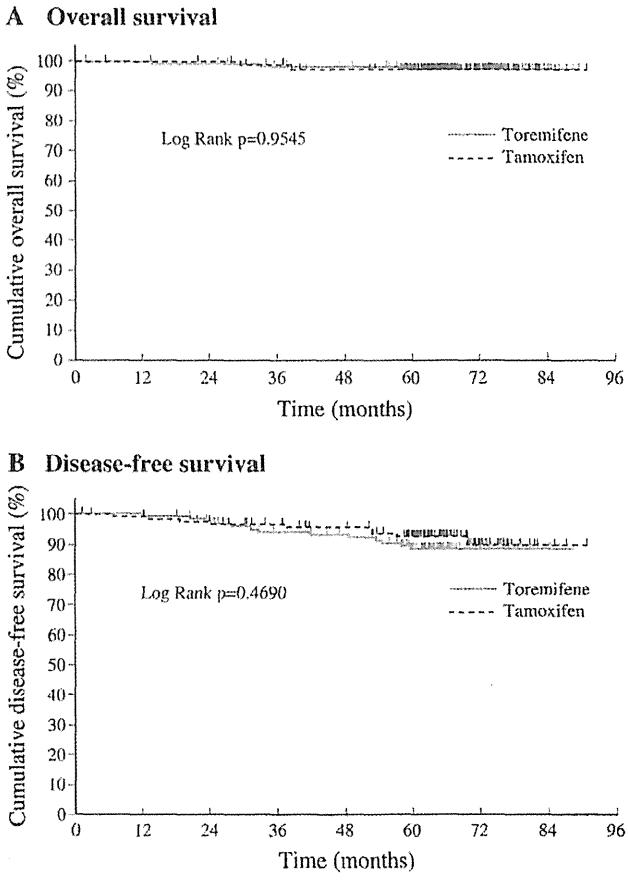

Fig. 2 Kaplan–Meier curves for overall survival (**a**) and disease-free survival (**b**)

observation date (3 in the toremifene group, 3 in the tamoxifen group), resulting in cumulative overall survival of 97.5 % in the toremifene group and 97.3 % in the tamoxifen group. These data indicated there was no significant difference between the two treatments (log-rank test; $P = 0.9458$). Thirteen patients in the toremifene group and 8 in the tamoxifen group relapsed before the end of follow-up, resulting in cumulative disease-free survival of 88.4 and 90.7 %, respectively. Thus, there were no significant differences between the two groups as determined by these secondary endpoints (log-rank test; $P = 0.3359$).

Effects on lipid profiles

The effects of the two agents on lipid profiles differed as described in detail elsewhere [11]. Compared with baseline, at 24 months, the toremifene group had significantly reduced TC and LDL-C levels, and significantly increased HDL-C levels. Their TG levels were not affected. The tamoxifen group ($N = 120$) also had significantly reduced TC and LDL-C levels; no significant changes occurred in HDL-C ($P = 0.297$) or TG levels ($P = 0.120$). Overall,

the effects of toremifene on lipid profile were more beneficial than those of tamoxifen.

Adverse events

The incidence of side effects (including subjective symptoms and objective opinions) was 31.7 % in the toremifene group and 33.3 % in the tamoxifen group. The most frequent treatment-related adverse events are shown in Table 2. Hot flashes and vaginal discharge were observed at high frequency in both groups. There were 2 patients of grade 4 in the toremifene group (endometrial cancer and uterine leiomyoma) and 1 in the tamoxifen group (cryptogenic organizing pneumonia). No coronary heart disease was observed; cataracts and endometrial cancers were rare, and there were no deaths due to adverse events. In clinical laboratory tests liver function was significantly worse in patients treated with toremifene than in those treated with tamoxifen.

Discussion

Before this study no randomized clinical studies had been conducted on Japanese patients comparing the clinical efficacy of toremifene and tamoxifen for postoperative adjuvant therapy of early breast cancer. We therefore conducted a phase III trial to demonstrate non-inferiority, with a 10 % non-inferiority margin, for a toremifene group against a tamoxifen group, using 5-year survival as the primary endpoint among Japanese patients. Our results verified the non-inferiority of toremifene compared with tamoxifen. The outcomes from this study also showed no significant differences between both groups for cumulative overall survival and cumulative disease-free survival, which were secondary endpoints. These results indicate that toremifene was as effective as tamoxifen in the adjuvant setting.

We used a 2-year treatment duration because this was the standard treatment duration in Japan for using tamoxifen in adjuvant settings for early breast cancer, although there have been reports concerning the optimum duration of tamoxifen treatment in European and North American trials [12, 13]. SERMs have been the major adjuvant therapy for postmenopausal breast cancer worldwide for decades. Holli et al. [14] first reported the clinical utility of toremifene, showing that overall survival and cumulative disease-free survival were equivalent to those for tamoxifen in the interim results of a trial on adjuvant therapy for postmenopausal stage II-IIIB breast cancer patients (459 in the toremifene group and 440 in the tamoxifen group). In addition, others have shown no significant differences between toremifene and tamoxifen, including a double-blind randomized trial in postmenopausal women with estrogen receptor-positive advanced breast cancer [15] and an international collaborative randomized trial of endocrine therapy for early-stage breast cancer patients [16]. In the latter trial, 5-year survival for the toremifene and tamoxifen groups was 85 and 81 %, respectively ($P = 0.83$), and 5-year disease-free survival was 72 and 69 %, respectively ($P = 0.64$). These results demonstrate that these two agents have equivalent efficacy. Recently, Lewis et al. [17] reported no significant differences in a randomized trial of toremifene and tamoxifen adjuvant therapy for 1813 North American patients with early breast cancer. After 59 months of follow-up, after 5 years of drug administration, median survival of the toremifene and tamoxifen groups was 98.6 and 98.1 months, respectively ($P = 0.628$) and median disease-free survival was 96.7 and 96.4 months, respectively ($P = 0.790$). Furthermore, a meta-analysis of five clinical trials of endocrine therapy as primary therapy for locally advanced and metastatic postmenopausal breast cancer [18] found that response and risk of death were identical for toremifene and tamoxifen. Taken together, these European and North American clinical trials convincingly demonstrate the equivalent treatment efficacy of toremifene and tamoxifen in Caucasians.

In recent years, SERMs have also attracted attention for their beneficial effects on serum lipids [19]. Consequently, we included the effects on serum lipid profiles as a secondary endpoint in this trial. We observed beneficial changes in serum lipids in both treatment groups post-administration, for example significant decreases in levels of TC and LDL-C. In addition, HDL-C significantly increased in patients receiving toremifene, in accordance with previously published results [6, 20]. There have been several reports that tamoxifen increased serum TG levels, whereas toremifene had little or no effect [6, 7]. Similar effects were observed in an in-vitro study of intracellular concentrations of TG in HepG2 cells [21]. In postmenopausal breast cancer patients, the effects of medications taken long-term on lipid and bone metabolism are important to the quality of life and are becoming an important criterion for selecting treatment. Of all serum lipids, only the level of HDL-C is correlated with coronary artery disease risk. Robins et al. [22] measured an 11 % reduction in coronary heart disease risk because of a 5 mg/dL increase in HDL-C. Moreover, hypertriglyceridemia is a well-known risk factor of arteriosclerosis in the USA, Europe, and Asia, including Japan [23, 24]. Although LDL reduction remains the main target of intervention for lipid-lowering, Barzi et al. [25] showed that among patients of the Asia–Pacific region, TG and HDL were better predictors of coronary heart disease and

Table 2 Treatment-related adverse events

Event	Toremifene (n = 126)					Tamoxifen (n = 126)					P value
	Grade 1	Grade 2	Grade 3	Grade 4	Total (%)	Grade 1	Grade 2	Grade 3	Grade 4	Total (%)	
Metabolic and nutritional disorders											
Reduced appetite (anorexia)	3	1			4 (3.2)	4				4 (3.2)	0.991
Nervous system disorders											
Dizziness	1	2			3 (2.4)	5	1			6 (4.8)	0.321
Headache	2				2 (1.6)	2				2 (1.6)	1.000
Other					0 (0)	3				3 (2.4)	0.082
Gynecological disorders											
Endometrial cancer				1	1 (0.8)					0 (0)	0.317
Uterine leiomyoma				1	1 (0.8)	1				1 (0.8)	0.996
Uterine polyps		1			1 (0.8)					0 (0)	0.317
Vaginal discharge	7	2			9 (7.1)	7	1			8 (6.3)	0.791
Genital hemorrhage	3	1			4 (3.2)	5				5 (4.0)	0.745
Cardiac disorders											
Palpitations	1				1 (0.8)	2				2 (1.6)	0.562
Eye disorders											
Visual impairment					0 (0)	2				2 (1.6)	0.157
Other					0 (0)	2				2 (1.6)	0.157
Vascular disorders											
Hot flashes	15	2	1		18 (14.3)	10	2			12 (9.5)	0.243
Peripheral coldness	1	1			2 (1.6)					0 (0)	0.157
Flushing					2 (1.6)					0 (0)	0.157
Skin and subcutaneous disorders											
Hyperhidrosis	6				6 (4.8)	2				2 (1.6)	0.152
Rash	3				3 (2.4)	1				1 (0.8)	0.314
Other	3				3 (2.4)	2				2 (1.6)	0.652
Gastrointestinal disorders											
Nausea	2	2			4 (3.2)	6				6 (4.8)	0.540
Gastritis					0 (0)	2	1			3 (2.4)	0.082
Other	1				1 (0.8)	7				7 (5.6)	0.031
Respiratory disorders											
Cryptogenic organizing pneumonia					0 (0)				1	1 (0.8)	0.317
General disorders											
Malaise	3	1			4 (3.2)	2				2 (1.6)	0.406
Feeling hot					0 (0)	1				1 (0.8)	0.317
Clinical laboratory tests											
GOT	12	9	4		23 (20.2)	5	5			10 (8.1)	0.006
GPT	9	10	5		24 (19.4)	2	7			9 (7.3)	0.005
ALP	1	1			2 (1.6)					0 (0)	0.157

GOT glutamic oxaloacetic transaminase, *GPT* glutamic–pyruvic transaminase, *ALP* alkaline phosphatase

cardiovascular disease risk than TC alone. Recently, Anan et al. [26] reported that toremifene is more beneficial than anastrozole, a widely used non-steroidal aromatase inhibitor, on lipid profiles and bone metabolism in Japanese postmenopausal females with early breast cancer. Therefore, toremifene is regarded as suitable for adjuvant therapy of breast cancer patients with dyslipidemia requiring long-term medication.

Regarding drug safety and tolerance, the incidence of subjective and objective side effects was similar in both groups in our study. Both groups had a high frequency of known treatment-related adverse events, for example hot flashes and vaginal discharge, most likely because of the weak pro-estrogen effect of these SERMs. In the adjuvant setting, second non-breast primary cancers are very important concern. One endometrial cancer was observed. No significant difference between those taking toremifene or tamoxifen in the occurrence of endometrial cancer has been reported in previous trials [17]. No serious treatment-related adverse events, for example coronary artery disease associated with dyslipidemia, were observed. Although cataracts and endometrial cancers were reported in the European and American clinical trials [27, 28], these adverse events were rare in our study. These results suggest there may be ethnic differences between Japanese and Caucasians in the metabolism and effects of SERMs. The frequencies of abnormal findings in clinical tests were 31.7 and 39.7 % in the toremifene and tamoxifen groups, respectively. The most common adverse event in either group was an increase in liver function test values. Our results showed that liver function was significantly worse in patients treated with toremifene than in those treated with tamoxifen. For most patients, elevated levels of transaminases were promptly restored to baseline levels after stopping the treatment with toremifene. The difference between toremifene and tamoxifen in the effects on liver function has not been reported after previous studies. There might be ethnic differences in the metabolism of toremifene between Japanese and Caucasians. Further research is required to confirm this. Recently, meta-analysis performed by Zhou et al. [29] indicated that toremifene is as effective and as safe as tamoxifen in the adjuvant setting. Although our results are in general agreement with this, our results suggested some differences among the two agents.

One limitation of this study is the relatively small number of patients enrolled, although the study outcome confirmed the non-inferiority of toremifene to tamoxifen. Another is the treatment duration; throughout the world the standard duration of treatment with SERMs is currently 5 years, although no Japanese randomized study has shown the advantages of using tamoxifen for 5 years over 2 years. Sequential treatment (e.g., 2–3 years treatment with tamoxifen followed by aromatase inhibitors) is also widely used today. Because the optimum duration of treatment with SERMs in sequential treatment has not yet been established, the outcomes of this study should contribute to current clinical practice of breast cancer management. Further large-size investigation is necessary to substantiate the optimum treatment for Japanese patients in an adjuvant setting.

In conclusion, we have shown that the efficacy and safety of toremifene are equivalent to those of tamoxifen for postmenopausal Japanese patients with early breast cancer; however, toremifene may be more beneficial for patients with dyslipidemia, because of its effects on the serum lipid profile.

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Conflict of interest The authors indicated no potential conflict of interest.

Appendix

See Table 3.

Table 3 Participating institutions

Hokkaido University Hospital	Cancer Institute Hospital	Osaka University Hospital
NHO Hokkaido Cancer Center	NHO Yokohama Medical Center	Osaka City General Hospital
Sapporo Medical University Hospital	Kanagawa Cancer Center	Kansai Rosai Hospital
NHO Sendai Medical Center	Fukui Red Cross Hospital	Kinki University Hospital
Tohoku Kosai Hospital	Shinshu University Hospital	Kobe University Hospital
Fukushima Medical University Hospital	Ogaki Municipal Hospital	Kinki Central Hospital
Gunma University Hospital	Shizuoka General Hospital	Okayama University Hospital
Gunma Prefectural Cancer Center	Nagoya University Hospital	Kawasaki Medical School Hospital
Saitama Cancer Center	Nagoya City University Hospital	Tokushima University Hospital
Chiba Cancer Center	NHO Nagoya National Hospital	NHO Shikoku Cancer Center
Juntendo University Urayasu Hospital	Yokkaichi Municipal Hospital	Kitakyushu Municipal Medical Center