Table 1 Ongoing randomized trials testing the worth of local therapy for an intact primary in women with stage IV breast cancer

Country	Trial number	Accrual period	*n*	Initial therapy	Radiotherapy	Primary endpoint
India	NCT00193778	2005-12	350	Adriamycin-cytoxan	If indicated	Time to progression
Turkey	NCT00557986	2008-12	281	Surgery	For breast conservation	Survival
United States and Canada	NCT01242800	2011-16	368	Appropriate systemic therapy	Per standards for stage I-III	Survival
Netherlands	NCT01392586	2011-16	516	Surgery	For positive margins or palliation	2-yr survival
Austria	NCT01015625	2010-19	254	Surgery	Per standards for stage I-III	Survival
Japan	JCOG 1017	2011-16	410	Appropriate systemic therapy	No	Survival

JCOG: Japan Clinical Oncology Group; NCT number: A unique identification code given to each clinical study registered on ClinicalTrials.gov.

prognosis as a result of surgery)[15]. In addition, a study has reported a satisfactory prognosis for asymptomatic rather than symptomatic patients, regardless of whether treatment was administered and regardless of the type of treatment[16]. Results suggest that local control itself may act beneficially on prognosis, irrespective of whether treatment is classified as surgery, radiation, *etc.*

TRIALS CURRENTLY UNDERWAY TO DETERMINE THE USEFULNESS OF RESECTION OF THE PRIMARY TUMOR IN STAGE IV BREAST CANCER

As noted previously, there are absolutely no prospective data at the current time to corroborate the usefulness of resection of the primary tumor in stage IV breast cancer in terms of increasing survival time or improving local control. At the current time, there is no evidence actively in favor of such a resection. That said, many results of retrospective studies continue to be discussed in various fora. In the absence of robust evidence, this meta-analysis provides an evidence base for primary resection in the setting of stage IV breast cancer for appropriately selected patients[17]. Resection of the primary tumor could greatly affect breast cancer care so this clinical question needs to be answered in prospective trials. Given this potential, 6 groups are currently enrolling patients[18-20] (Table 1). The first reports of two prospective studies were indicated in the San Antonio Breast Cancer Symposium 2013[21,22]. Both studies did not demonstrate a significant survival benefit of primary surgery. From the Indian trial, the distant disease free survival in the patients with surgery was significantly worse than that of the patients without surgery. One of the reasons was the insufficient systemic chemotherapy after surgery. They did not continue systemic chemotherapy after randomization and appropriate systemic therapies according to breast cancer subtypes were not selected in these protocols. So, the median survival time was shorter than that of retrospective European and American data. In particular, they did not use molecular target therapy for patients with human epidermal growth factor receptor type 2 positive breast cancer. Moreover, the diagnosis of metastasis was uncertain. They only used bone scintigraphy to diagnose a solitary bone metastasis. The Breast Cancer Study Group of the Japan Clinical Oncology Group (1017) and Eastern Clinical Oncology Group (2108) began enrolling patients for a phase 3 trial in June 2011[23]. Patients receive current standard systemic therapy before and after randomization and the latest imaging examination before treatment in these trials. A trial by the current authors is determining the significance of early resection of the primary tumor in stage IV breast cancer when that tumor can be controlled by medication. Items being assessed include the total survival time as well as the significance of local control; the results of the trial are sure to provide clinically significant evidence.

CONCLUSION

At the current point in time, one cannot say whether or not resection of the primary tumor provides a clear benefit in the management of stage IV breast cancer. Basic studies have revealed the biology of breast cancer in detail and the role of surgery is changing as treatment is better tailored to the individual in accordance with the individual's biology. The goal of treatment has to be clearly identified: increase the patient's survival time, provide local control or perform histology to determine the cancer's properties. Without a doubt, the best evidence is absolutely essential to treat patients who need surgery at the right time. Announcement of the results of clinical trials that are currently underway and examination of those results in detail are the first steps to obtain that evidence. However, obtaining results takes time and other strategies to treat breast cancer are constantly changing. In addition, the drugs used and patient attributes differ completely in different countries. An effective strategy to treat stage IV breast cancer must be devised in accordance with medication in light of the patient's symptoms while remaining mindful of the significance of surgery.

REFERENCES

1 **Ohsumi S**, Inoue T, Kiyoto S, Hara F, Takahashi M, Takabatake D, Takashima S, Aogi K, Takashima S. Detection of isolated ipsilateral regional lymph node recurrences by F18-fluorodeoxyglucose positron emission tomography-CT in follow-up of postoperative breast cancer patients. *Breast Cancer Res Treat* 2011; **130**: 267-272 [PMID: 21590272 DOI: 10.1007/s10549-011-1561-8]

2 **Niikura N**, Costelloe CM, Madewell JE, Hayashi N, Yu TK,

Liu J, Palla SL, Tokuda Y, Theriault RL, Hortobagyi GN, Ueno NT. FDG-PET/CT compared with conventional imaging in the detection of distant metastases of primary breast cancer. *Oncologist* 2011; **16**: 1111-1119 [PMID: 21765193 DOI: 10.1634/theoncologist.2011-0089]

3 **Pagani O**, Senkus E, Wood W, Colleoni M, Cufer T, Kyriakides S, Costa A, Winer EP, Cardoso F. International guidelines for management of metastatic breast cancer: can metastatic breast cancer be cured? *J Natl Cancer Inst* 2010; **102**: 456-463 [PMID: 20220104 DOI: 10.1093/jnci/djq029]

4 **Petrelli F**, Barni S. Surgery of primary tumors in stage IV breast cancer: an updated meta-analysis of published studies with meta-regression. *Med Oncol* 2012; **29**: 3282-3290 [PMID: 22843291 DOI: 10.1007/s12032-012-0310-0]

5 **Ruiterkamp J**, Voogd AC, Bosscha K, Tjan-Heijnen VC, Ernst MF. Impact of breast surgery on survival in patients with distant metastases at initial presentation: a systematic review of the literature. *Breast Cancer Res Treat* 2010; **120**: 9-16 [PMID: 20012891 DOI: 10.1007/s10549-009-0670-0]

6 **Shien T**, Kinoshita T, Shimizu C, Hojo T, Taira N, Doihara H, Akashi-Tanaka S. Primary tumor resection improves the survival of younger patients with metastatic breast cancer. *Oncol Rep* 2009; **21**: 827-832 [PMID: 19212646]

7 **Rapiti E**, Verkooijen HM, Vlastos G, Fioretta G, Neyroud-Caspar I, Sappino AP, Chappuis PO, Bouchardy C. Complete excision of primary breast tumor improves survival of patients with metastatic breast cancer at diagnosis. *J Clin Oncol* 2006; **24**: 2743-2749 [PMID: 16702580 DOI: 10.1200/JCO.2005.04.2226]

8 **Neuman HB**, Morrogh M, Gonen M, Van Zee KJ, Morrow M, King TA. Stage IV breast cancer in the era of targeted therapy: does surgery of the primary tumor matter? *Cancer* 2010; **116**: 1226-1233 [PMID: 20101736 DOI: 10.1002/cncr.24873]

9 **Paget S**. The distribution of secondary growths in cancer of the breast. *Lancet* 1889; **133**: 571-573 [DOI: 10.1016/S0140-6736(00)49915-0]

10 **Budd GT**, Cristofanilli M, Ellis MJ, Stopeck A, Borden E, Miller MC, Matera J, Repollet M, Doyle GV, Terstappen LW, Hayes DF. Circulating tumor cells versus imaging--predicting overall survival in metastatic breast cancer. *Clin Cancer Res* 2006; **12**: 6403-6409 [PMID: 17085652 DOI: 10.1158/1078-0432.CCR-05-1769]

11 **Danna EA**, Sinha P, Gilbert M, Clements VK, Pulaski BA, Ostrand-Rosenberg S. Surgical removal of primary tumor reverses tumor-induced immunosuppression despite the presence of metastatic disease. *Cancer Res* 2004; **64**: 2205-2211 [PMID: 15026364 DOI: 10.1158/0008-5472.CAN-03-2646]

12 **Flanigan RC**, Salmon SE, Blumenstein BA, Bearman SI, Roy V, McGrath PC, Caton JR, Munshi N, Crawford ED. Nephrectomy followed by interferon alfa-2b compared with interferon alfa-2b alone for metastatic renal-cell cancer. *N Engl J Med* 2001; **345**: 1655-1659 [PMID: 11759643 DOI: 10.1056/NEJMoa003013]

13 **Kakarala M**, Wicha MS. Implications of the cancer stem-cell hypothesis for breast cancer prevention and therapy. *J Clin Oncol* 2008; **26**: 2813-2820 [PMID: 18539959 DOI: 10.1200/JCO.2008.16.3931]

14 **Kim MY**, Oskarsson T, Acharyya S, Nguyen DX, Zhang XH, Norton L, Massagué J. Tumor self-seeding by circulating cancer cells. *Cell* 2009; **139**: 1315-1326 [PMID: 20064377 DOI: 10.1016/j.cell.2009.11.025]

15 **Lang JE**, Tereffe W, Mitchell MP, Rao R, Feng L, Meric-Bernstam F, Bedrosian I, Kuerer HM, Hunt KK, Hortobagyi GN, Babiera GV. Primary tumor extirpation in breast cancer patients who present with stage IV disease is associated with improved survival. *Ann Surg Oncol* 2013; **20**: 1893-1899 [PMID: 23306905 DOI: 10.1245/s10434-012-2844-y]

16 **Hazard HW**, Gorla SR, Scholtens D, Kiel K, Gradishar WJ, Khan SA. Surgical resection of the primary tumor, chest wall control, and survival in women with metastatic breast cancer. *Cancer* 2008; **113**: 2011-2019 [PMID: 18780312 DOI: 10.1002/cncr.23870]

17 **Khan SA**. Surgery for the intact primary and stage IV breast cancer...lacking "robust evidence". *Ann Surg Oncol* 2013; **20**: 2803-2805 [PMID: 23649932 DOI: 10.1245/s10434-013-3002-x]

18 **Perez CB**, Khan SA. Local therapy for the primary breast tumor in women with metastatic disease. *Clin Adv Hematol Oncol* 2011; **9**: 112-119 [PMID: 22173605]

19 **Soran A**, Ozbas S, Kelsey SF, Gulluoglu BM. Randomized trial comparing locoregional resection of primary tumor with no surgery in stage IV breast cancer at the presentation (Protocol MF07-01): a study of Turkish Federation of the National Societies for Breast Diseases. *Breast J* 2009; **15**: 399-403 [PMID: 19496782 DOI: 10.1111/j.1524-4741.2009.00744.x]

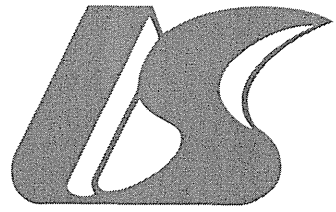
20 **Ruiterkamp J**, Voogd AC, Tjan-Heijnen VC, Bosscha K, van der Linden YM, Rutgers EJ, Boven E, van der Sangen MJ, Ernst MF. SUBMIT: Systemic therapy with or without up front surgery of the primary tumor in breast cancer patients with distant metastases at initial presentation. *BMC Surg* 2012; **12**: 5 [PMID: 22469291 DOI: 10.1186/1471-2482-12-5]

21 **Badwe R**, Parmar V, Hawaldar R, Nair N, Kaushik R, Siddique S, Navale A, Budrukkar A, Mittra I, Gupta S. San Antonio Breast Cancer Symposium. Abstract S2-02. San Antonio, USA, 2013

22 **Soran A**, Ozmen V, Ozbas S, Karanlik H, Muslumanoglu M, Igci A, Canturk Z, Utkan Z, Ozaslan C, Evrensel T, Uras C, Aksaz E, Soyder A, Ugurlu U, Col C, Cabioglu N, Bozkurt B, Dagoglu T, Uzunkoy A, Dulger M, Koksal N, Cengiz O, Gulluoglu B, Unal B, Atalay C, Yildirim E, Erdem E, Salimoglu S, Sezer A, Koyuncu A, Gurleyik G, Alagol H, Ulufi N, Berberoglu U, Kennard E, Kelsey S, Lembersky B. San Antonio Breast Cancer Symposium. Abstract S2-03. San Antonio, US, 2013

23 **Shien T**, Nakamura K, Shibata T, Kinoshita T, Aogi K, Fujisawa T, Masuda N, Inoue K, Fukuda H, Iwata H. A randomized controlled trial comparing primary tumour resection plus systemic therapy with systemic therapy alone in metastatic breast cancer (PRIM-BC): Japan Clinical Oncology Group Study JCOG1017. *Jpn J Clin Oncol* 2012; **42**: 970-973 [PMID: 22833684 DOI: 10.1093/jjco/hys120]

P- Reviewers: Braga S, Mazzocchi M, Mego M
S- Editor: Wen LL **L- Editor**: Roemmele A **E- Editor**: Liu SQ



百世登

Baishideng®

Published by **Baishideng Publishing Group Co., Limited**
Flat C, 23/F., Lucky Plaza, 315-321 Lockhart Road,
Wan Chai, Hong Kong, China
Fax: +852-31158812
Telephone: +852-58042046
E-mail: bpgoffice@wjgnet.com
http://www.wjgnet.com

Cancer Chemother Pharmacol (2014) 74:603–609
DOI 10.1007/s00280-014-2545-2

ORIGINAL ARTICLE

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

Tadahiko Shien · Hiroji Iwata · Takashi Fukutomi · Kenichi Inoue · Kenjiro Aogi · Takayuki Kinoshita · Jiro Ando · Seiki Takashima · Kenichi Nakamura · Taro Shibata · Haruhiko Fukuda

Received: 9 June 2014 / Accepted: 12 July 2014 / Published online: 24 July 2014

Abstract

Purpose A prospective randomized clinical trial was conducted to evaluate the efficacy of tamoxifen plus doxorubicin and cyclophosphamide compared to tamoxifen plus tegafur-uracil as an adjuvant therapy to treat node-positive premenopausal breast cancer (PreMBC).

Methods Eligibility criteria included pathologically node-positive (n = 1–9) preMBC with curative resection, in stages I–IIIA. Patients were randomized to receive either tamoxifen 20 mg/day plus tegafur-uracil 400 mg/day (TU) for 2 years or six courses of a 28-day cycle of doxorubicin 40 mg/m^2 plus cyclophosphamide 500 mg/m^2 on day 1 along with tamoxifen (ACT) given for 2 years as adjuvant therapy. Primary endpoint was overall survival (OS), and secondary endpoint was recurrence-free survival (RFS).

Results In total, 169 patients were recruited (TU arm 87, ACT arm 82) between October 1994 and September 1999. The HR for OS was 0.76 (95 % CI 0.35, 1.66, log-rank p = 0.49) and that for RFS was 0.77 (95 % CI 0.44, 1.36, log-rank p = 0.37), with ACT resulting in a better HR. The 5-year OS was 79.7 % for patients in the TU arm and 83 % for those in the ACT arm. The 5-year RFS was 66.1 % for patients in the TU arm and 70.6 % for those in the ACT arm. A higher proportion of patients in the ACT arm experienced grade 3 leucopenia (0 % in the TU arm, 4 % in the ACT arm).

Conclusions There were no significant differences in the efficacy of TU and ACT as adjuvant therapy.

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

On behalf of the JCOG Breast Cancer Study Group.

T. Shien (✉)
Department of Breast and Endocrine Surgery, Okayama University Hospital, Okayama 700-8558, Japan
e-mail: tshien@md.okayama-u.ac.jp

H. Iwata
Department of Breast Oncology, Aichi Cancer Center Hospital, Nagoya 464-8681, Japan

T. Fukutomi · T. Kinoshita
Department of Breast Surgery, National Cancer Center Hospital, Tokyo 104-0045, Japan

K. Inoue
Department of Medical Oncology, Saitama Cancer Center, Saitama 362-0806, Japan

K. Aogi · S. Takashima
Department of Surgery, National Hospital Organization Shikoku Cancer Center, Matsuyama 791-0280, Japan

J. Ando
Department of Breast Surgery, Tochigi Cancer Center, Utsunomiya 320-0834, Japan

K. Nakamura · T. Shibata · H. Fukuda
JCOG Data Center, Multi-institutional Clinical Trial Support Center, National Cancer Center, Tokyo 104-0045, Japan

Introduction

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

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

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

Patients and methods

Eligibility and excluding criteria

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

Planned treatment schedules

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

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

Patient assessment

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

Study endpoint

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

Statistical analysis plan

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

recommended as the new standard treatment. The estimated 5-year OS of these patients is commonly 64–88 % [4–6]. A total of 342 patients were needed to detect a prolongation of the 5-year OS from 75 % for patients in the TU arm to 85 % for patients in ACT arm with an 80 % power and a two-sided alpha of 5 %. Considering some patients potentially lost to follow-up, the sample size was set at 400 patients in total. The planned study period was originally 2 years for recruitment and an additional 5 years for follow-up. Due to the slow recruitment, the protocol was revised to extend the recruitment period, and the sample size was revised to 330 patients with a recruitment period of 5 years. OS was analyzed for all randomized patients and RFS for randomized patients excluding a patient with bone metastasis at the registration. OS and RFS were estimated using the Kaplan–Meier method, and curves were compared using a log-rank test. Hazard ratios of treatment effects were estimated by a Cox regression model. All analyses were based on intent to treat. All statistical analyses were performed using SAS release 8.2 (SAS Institute, Cary, NC).

Interim analysis and monitoring plan

An interim analysis was to be performed when half of the total number of patients was enrolled. The JCOG Data and Safety Monitoring Committee (DSMC) independently reviewed the interim analysis report, and premature termination of the trial could be considered at that stage. In-house interim monitoring was performed by the JCOG Data Center to ensure data submission, patient eligibility, protocol compliance, safety, and on-schedule study progress. The monitoring reports were submitted to and reviewed by the DSMC every 6 months.

Results

This study began in 1994. At an interim analysis on June 1999, patient recruitment was so slow that the DSMC recommended terminating patient recruitment or continuing but changing the primary endpoint to RFS. Furthermore, a consensus meeting in St. Gallen in 1997 deemed that administering tamoxifen to hormone receptor-negative patients was ethically unacceptable [7]. Therefore, recruitment of patients was terminated pursuant to suggestions from the JCOG DSMC.

In total, 169 patients were recruited and randomly assigned (Fig. 1). Four patients were ineligible because two were enrolled after starting protocol treatment, one had been diagnosed with bone metastasis, and the other was postmenopausal before recruitment, but these patients were included in the analysis. The two groups had highly similar baseline characteristics (Table 1). The median age was 46 years (30–56 years). One hundred and seventeen patients (69.2 %) had node metastases involving 1–3 nodes, while 52 (30.8 %) had node metastases involving 4–9 nodes. There were 59 patients (34.9 %) with ER- or PR-tumors, including patients with an unknown hormone status. Most patients (95.3 %) underwent total or radical mastectomy. Eighty-seven patients were assigned to the TU arm, and 82 patients were assigned to the ACT arm. Patient's diagram was shown in Fig. 1. The protocol treatment in the TU arm was completed by 75 of 87 patients (86.2 %), and the protocol treatment in the ACT arm was completed by 66 of 82 patients (80.5 %).

Survival

There were no significant differences in OS for patients in the two arms ($p = 0.494$, hazard ratio 0.76, 95 % confidence interval [CI] 0.35–1.66) (Fig. 2a). The 3- and 5-year OS were 90.3 and 79.7 % for patients in the TU arm and 90.6 and 83.0 % for patients in the ACT arm, respectively. There were no significant differences in RFS for patients in the two arms ($p = 0.37$, HR: 0.77, 95 % CI 0.44–1.36) (Fig. 2b). The 3- and 5-year RFS were 74.0 and 66.1 % for patients in the TU arm and 76.7 and 70.6 % for patients in the ACT arm, respectively.

Subgroup analysis was performed according to hormone receptor status. There were 57 patients (65.5 %) who were ER+ and/or PR+ in the TU arm and 52 (63.4 %) in the ACT arm. The OS curve is shown in Fig. 3a. Both ER- and PR-negative patients had a worse prognosis than ER-positive patients. However, patients in the TU and ACT arms had a similar OS, regardless of hormone status. Both ER- and PR-negative patients in the TU arm had a relatively shorter RFS than those in the ACT arm (Fig. 3b). There were no differences in the RFS of ER+ and/or PR+ patients in both arms.

Safety profile

Safety profiles are listed in Table 2A and B. Only one patient was observed grade 4 adverse event (GPT elevation) in the TU arm. This event was diagnosed at 35th day after the start of TU, and once the administration of UFT was halted, GPT decreased to normal levels. A higher proportion of patients in the ACT arm had a lower white blood cell count that was rated grade 3 (0 % in the TU arm, 3.8 % in the ACT arm), and a higher proportion of patients in the TU arm had elevated total bilirubin, GOT, and GPT that were rated grade 3 (12.6, 2.3, and 2.3 % in the TU arm, 0, 1.3, and 1.3 % in the ACT arm) and lower hemoglobin (3.4 % in the TU arm, 0 % in the ACT arm). A non-hematological toxicity (grade 3 nausea) was noted only in patients in the ACT arm (10 %). There was grade 3 rash (1.2 %) in a patient in the TU arm and grade 3 arrhythmia (1.3 %) in a patient in the ACT arm.

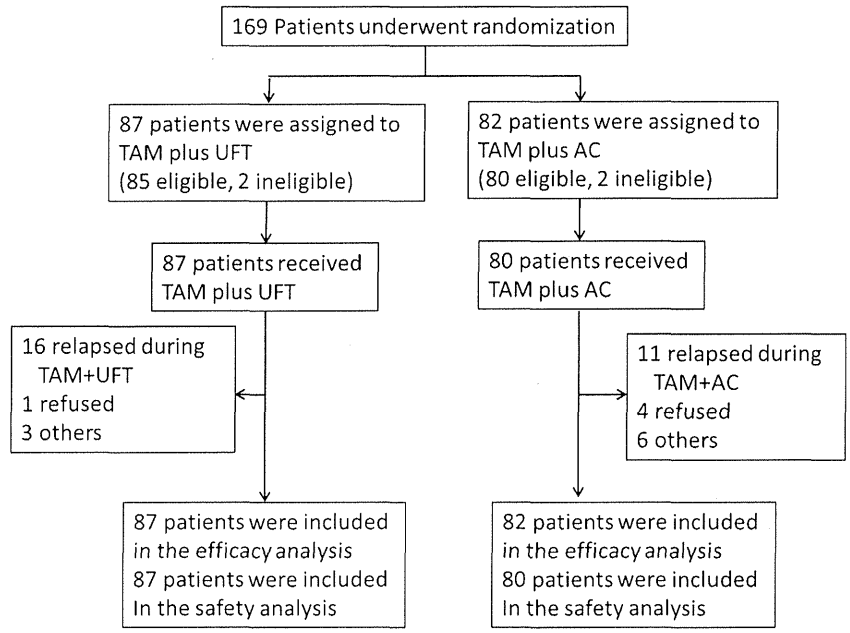


Fig. 1 Trial profile of Japan Clinical Oncology Group study, JCOG 9404

Table 1 Patient characteristics

Characteristics	TU ($n = 87$)	ACT ($n = 82$)
Age (year)		
Median	47	45
Range	31–55	30–56
No. of positive axillary nodes		
1–3	59	58
4–9	28	24
ER and/or PgR		
Negative/unknown	29	30
Positive	58	52
HER2		
Negative/unknown	70	63
Positive	17	19
Stage		
I	12	12
II	58	60
IIIA	17	11
Operation		
Radical mastectomy	1	6
Total mastectomy	81	73
Partial resection	5	3

Discussion

The decision to administer postoperative adjuvant drug therapy, which seeks to inhibit the recurrence of breast cancer, is often currently made based on the primary tumor's subtype. Breast cancer is essentially categorized

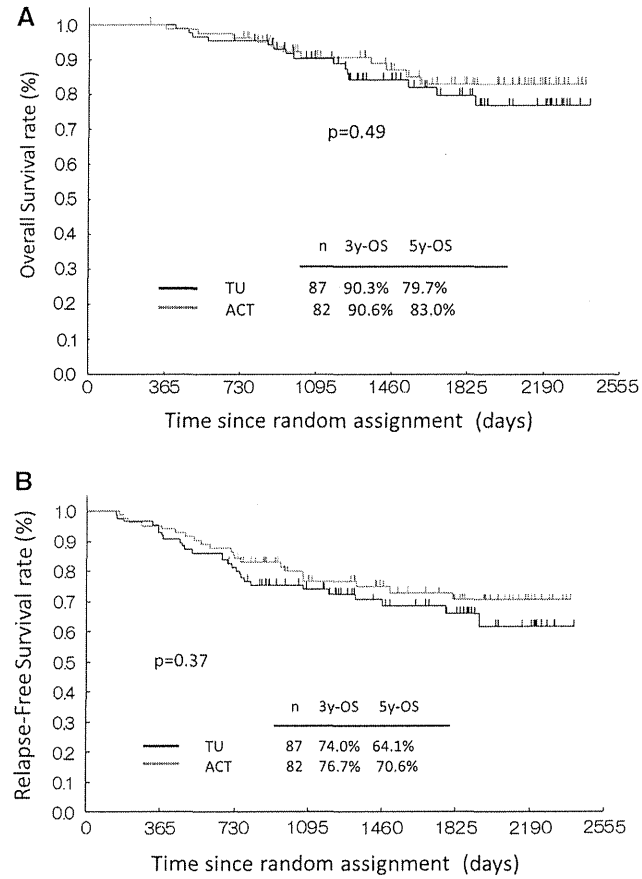


Fig. 2 Kaplan–Meier curves of overall survival (**a**) and relapse-free survival (**b**) for node-positive breast cancer patients treated with tamoxifen plus tegafur-uracil or tamoxifen with anthracycline and cyclophosphamide

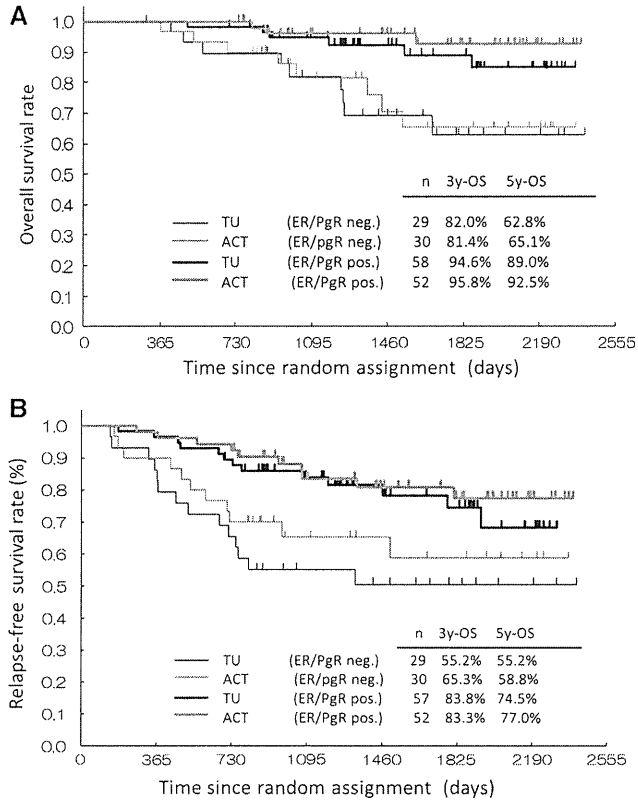


Fig. 3 Kaplan–Meier curves of overall survival (**a**) and relapse-free survival (**b**) for node-positive breast cancer patients treated with tamoxifen plus tegafur-uracil or tamoxifen with anthracycline and cyclophosphamide according to estrogen receptor (ER) and progesterone receptor (PgR) status

into four subtypes depending on the expression of ER, PgR, HER2, and Ki67 [2]. Endocrine drugs are given to patients with ER- and/or PgR-positive luminal tumors. Trastuzumab (a molecular-targeted agent) and an anticancer agent are both administered to HER2-positive patients. These strategies are tailor-made target therapies according to the prediction of efficacy of drugs. In addition to endocrine drugs, anticancer agents are often administered to patients with breast cancer expressing a high level of Ki67 [8, 9]. The individual determination of whether or not a tumor is sensitive to a drug is difficult, and despite this, anticancer agents are administered. Including anticancer agents is considered acceptable when patients have numerous lymph node metastases (irrespective of tumor subtype), if their cancer is ER- and/or PgR-positive and expressing a low level of Ki67. The validity and evaluation of Ki-67 are not definitive [10]. Both anthracycline and taxane are often administered sequentially for these patients despite the possibility that efficacy of these drugs is low. These classifications of breast cancer and administration of taxane and molecular drugs were widely in use after the current trial began.

Table 2 Hematological (A) and non-hematological (B) toxicities

Toxicities	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)
(A)			
TU			
WBC	8 (9)	0 (0)	0 (0)
Hb	2 (2)	3 (3)	0 (0)
T-bill	43 (49)	11 (13)	0 (0)
GOT	5 (6)	2 (2)	0 (0)
GPT	9 (10)	2 (2)	1 (1)
ACT			
WBC	12 (14)	3 (3)	0 (0)
Hb	7 (8)	0 (0)	–
T-bill	8 (9)	0 (0)	0 (0)
GOT	1 (1)	1 (1)	0 (0)
GPT	5 (6)	1 (1)	0 (0)
(B)			
TU			
Infection	0 (0)	0 (0)	0 (0)
Nausea/vomiting	7 (0)	0 (0)	–
Diarrhea	2 (0)	0 (0)	0 (0)
Arrhythmia	1 (1)	0 (0)	0 (0)
Thrombosis	0 (0)	0 (0)	0 (0)
Alopecia	0 (0)	–	–
Rush	2 (0)	1 (0)	0 (0)
ACT			
Infection	0 (0)	0 (0)	0 (0)
Nausea/vomiting	29 (36)	8 (10)	–
Diarrhea	1 (1)	0 (0)	0 (0)
Arrhythmia	1 (1)	1 (1)	0 (0)
Thrombosis	0 (0)	0 (0)	0 (0)
Alopecia	37 (46)	–	–
Rush	1 (1)	0 (0)	0 (0)

At the beginning of this study, tamoxifen was administered as the standard therapy even if the patient was ER-negative. In light of current evidence, there is no doubt that tamoxifen has little efficacy in treating ER-negative breast cancer [11], though there are also no data indicating that the efficacy of anticancer agents will diminish if used in combination with tamoxifen. Thus, the results of this trial simply compared taking UFT for 2 years to taking AC to treat node-positive premenopausal breast cancer. Previous meta-analyses clearly revealed data indicating that AC therapy is more effective at preventing recurrence than CMF [12–16], but AC therapy has not been compared to oral fluoropyrimidine. The results of this trial indicated no difference between oral fluoropyrimidine and AC therapy in terms of prolonging survival in patients overall. AC therapy resulted in a longer recurrence-free survival (RFS) in only ER-negative patients. These results do not have a meaning

for recent breast cancer treatment strategy, because of the insufficiency of patients recruitment and old adjuvant treatment design. However, this finding suggests that AC therapy has limited efficacy when treating node-positive breast cancer by administering tamoxifen as a postoperative adjuvant therapy to treat ER-positive breast cancer. This finding also suggests that administration of oral fluoropyrimidine alone may be sufficient in some cases. In fact, OS and PFS were similar between ACT and TU arm with ER-positive breast cancer. A potent anticancer agent, like anthracycline, may not be needed to treat ER-positive breast cancer even if it has lymph node metastasis.

The question of whether UFT is needed or if tamoxifen alone is sufficient remains. Results of the JCOG9401 study [17], which examined patients with postmenopausal breast cancer with lymph node metastasis during the same period as the current trial, may offer an answer. The study compared tamoxifen alone and ACT therapy to treat patients with node-positive breast cancer, and results indicated that ER-positive patients had a 5-year RFS of 59.3 % when given tamoxifen alone versus 76.9 % when given ACT therapy and a 5-year OS of 87.1 % when given tamoxifen alone versus 90 % when given ACT therapy. Patients in this trial who were given UFT+tamoxifen had a 5-year RFS of 74.5 % and a 5-year OS of 89 %. There was possibility of prognostic benefit of additional UFT for ER-positive node-positive patients. Thus, comparison of TU therapy to tamoxifen alone is needed. In Japan, a prospective clinical trial on adding S-1 to treat patients with ER-positive breast cancer after completion of standard chemotherapy is currently enrolling subjects (UMIN000003969).

No major differences were noted in ER-negative patients in either arm of this trial. That said, ER-negative patients had a 5-year OS and a 5-year RFS that was about 30 % shorter than the 5-year OS and 5-year RFS of ER-positive patients. Trastuzumab tends to be administered to patients with ER-negative breast cancer if they are HER2-positive [18], and taxane tends to be administered along with anthracycline if they are HER2-negative [14]. The regimens in this trial were inadequate to evaluate the appropriate adjuvant drugs for ER-negative patients with node metastases.

In terms of adverse events, a hematological event in the form of a grade 3 decline in the white blood cell count was noted only in patients in the ACT arm. In terms of non-hematological events, abnormal liver function was noted in patients in the TU arm and nausea was often noted in patients in the ACT arm. Results of this trial revealed numerous adverse events in patients in the ACT arm as a whole. Since the current dose of AC is higher than that used in this trial, UFT may be less damaging. However, results suggested that sufficient caution in abnormal liver function is necessary to use UFT for long time as adjuvant therapy. The current trial did not administer both endocrine therapy and chemotherapy concurrently. Previous data on such chemoendocrine therapy have highlighted the enhancement of adverse events and an increase in thrombosis in particular [19–21]. Neither group of patients in this trial had thrombosis/embolism. Existing data are from the USA and Europe, where thrombosis is more prevalent. These conditions may pose far less of a problem in Japan because of their different physique. Chemoendocrine therapy is ruled out based on current data from Europe and the USA, but there may be leeway for therapy selection depending on the patient.

This trial prospectively studied the usefulness of ACT therapy to treat patients with node-positive premenopausal breast cancer. This trial began prior to 2000, and modern standard adjuvant therapy was established during collecting patients for this trial. There were some issues with trial design and trial enrollment since the standard therapy changed substantially during trial enrollment. However, the times changed from an era of actively administering anticancer agents to every patient with breast cancer with lymph node metastasis to an era of selecting therapy by predicting drug efficacy. Postoperative adjuvant therapy with oral FU was the standard therapy in this trial, and a new appreciation for the efficacy of that therapy is developing. In this trial, ACT did not significantly prolong survival compared to TUFT, especially in ER-positive patients. Without a doubt, these findings pose clinical questions that should be answered when formulating a treatment strategy for postoperative adjuvant therapy. Further studies via prospective trials (which include those currently underway) are needed.

Acknowledgments The authors wish to acknowledge the great contribution to this study by Ms. K. Minamoto with regard to data management and statistical analysis.

References

1. Kasumi F, Yoshimoto M, Uchino J et al (2003) Meta-analysis of five studies on tegafur plus uracil (UFT) as post-operative adjuvant chemotherapy for breast cancer. Oncology 64(2):146–153
2. Noguchi S, Koyama H, Uchino J et al (2005) Postoperative adjuvant therapy with tamoxifen, tegafur plus uracil, or both in women with node-negative breast cancer: a pooled analysis of six randomized controlled trials. J Clin Oncol 23(10):2172–2184
3. Tadashi Ikeda (1990) Adjuvant therapy of breast cancer. Jpn J Breast Cancer 5:215–226
4. Goldhirsch A, Winer EP, Coates AS et al (2013) Personalizing the treatment of women with early breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2013. Ann Oncol 24(9):2206–2223

5. Tobinai K, Kohno A, Shimada Y et al (1993) Toxicity grading criteria of the Japan Clinical Oncology Group. The Clinical Trial Review Committee of the Japan Clinical Oncology Group. Jpn J Clin Oncol 23(4):250–257
6. Gelber RD, Goldhirsch A (1986) A new endpoint for the assessment of adjuvant therapy in postmenopausal women with operable breast cancer. J Clin Oncol 4:1772–1779
7. Boccardo F, Rubagotti A, Amoroso D et al (1992) Chemotherapy versus tamoxifen versus chemotherapy plus tamoxifen in node positive, oestrogen receptor positive breast cancer patient. An update at 7 years of the 1st GROCTA trial. Eur J Cancer 28:673–680
8. Colozza M, Azambuja E, Cardoso F et al (2005) Proliferative markers as prognostic and predictive tools in early breast cancer: where are we now? Ann Oncol 16(11):1723–1739
9. de Azambuja E, Cardoso F, De Castro G Jr et al (2007) Ki-67 as prognostic marker in early breast cancer: a meta-analysis of published studies involving 12,155 patients. Br J Cancer 96(10):1504–1513
10. Dowsett M, Nielsen TO, A'Hern R et al (2011) Assessment of Ki67 in breast cancer: recommendations from the International Ki67 in Breast Cancer working group. J Natl Cancer Inst 103(22):1656–1664
11. Pearson OH, Hubay CA, Gordon NH et al (1989) Endocrine versus endocrine plus five-drug chemotherapy in postmenopausal women with stage II estrogen receptor positive breast cancer. Cancer 64:1819–1823
12. Early Breast Cancer Trialists' Collaborative Group (1998) Polychemotherapy for early breast cancer: an overview of the randomized trials. Lancet 352:930–942
13. Early Breast Cancer Trialists' Collaborative Group (1998) Tamoxifen for early breast cancer: an overview of the randomized trials. Lancet 351(9114):1451–1467
14. Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Peto R, Davies C, Godwin J, Gray R et al (2012) Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100,000 women in 123 randomised trials. Lancet 379(9814):432–444
15. Fisher B, Brown AM, Dimitrov NV et al (1990) Two months of doxorubicin-cyclophosphamide with and without interval reinduction therapy compared with 6 months of cyclophosphamide, methotrexate, and fluorouracil in positive-node breast cancer patients with tamoxifen-nonresponsive tumors: results from the National Surgical Adjuvant Breast and Bowel Project B-15. J Clin Oncol 8(9):1483–1496
16. Fisher B, Anderson S, Tan-Chiu E et al (2001) Tamoxifen and chemotherapy for axillary node-negative, estrogen receptor-negative breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-23. J Clin Oncol 19(4):931–942
17. Shien T, Iwata H, Aogi K et al (2014) Tamoxifen versus tamoxifen plus doxorubicin and cyclophosphamide as adjuvant therapy for node-positive postmenopausal breast cancer: results of a Japan Clinical Oncology Group Study (JCOG9401). Int J Clin Oncol [Epub ahead of print]
18. Moja L, Tagliabue L, Balduzzi S, et al (2012) Trastuzumab containing regimens for early breast cancer. Cochrane Database Syst Rev 18(4):CD006243
19. Pritchard KI, Paterson AH, Paul NA et al (1996) Increased thromboembolic complications with concurrent tamoxifen and chemotherapy in a randomized trial of adjuvant therapy for women with breast cancer. National Cancer Institute of Canada Clinical Trials Group Breast Cancer Site Group. J Clin Oncol 14(10):2731–2737
20. Pico C, Martin M, Jara C et al (2004) Epirubicin-cyclophosphamide adjuvant chemotherapy plus tamoxifen administered concurrently versus sequentially: randomized phase III trial in postmenopausal node-positive breast cancer patients. A GEICAM 9401 study. Ann Oncol 15(1):79–87
21. Goldhirsch A, Glick JH, Gelber RD et al (2001) Meeting highlights: international consensus panel on the treatment of primary breast cancer. Seventh international conference on adjuvant therapy of primary breast cancer. J Clin Oncol 19(18):3817–3827

Cancer Chemother Pharmacol (2014) 74:229–238
DOI 10.1007/s00280-014-2492-y

ORIGINAL ARTICLE

A phase II study of metronomic paclitaxel/cyclophosphamide/capecitabine followed by 5-fluorouracil/epirubicin/cyclophosphamide as preoperative chemotherapy for triple-negative or low hormone receptor expressing/HER2-negative primary breast cancer

N. Masuda · K. Higaki · T. Takano · N. Matsunami · T. Morimoto · S. Ohtani · M. Mizutani · T. Miyamoto · K. Kuroi · S. Ohno · S. Morita · M. Toi

Received: 7 November 2013 / Accepted: 14 May 2014 / Published online: 29 May 2014

Abstract

Purpose Better treatments for triple-negative breast cancer (TNBC) are needed. To address this need, we studied the effects of preoperative metronomic paclitaxel/cyclophosphamide/capecitabine (mPCX) followed by 5-fluorouracil (FU)/epirubicin/cyclophosphamide (FEC) as preoperative chemotherapy in TNBC patients.

Methods Forty primary TNBC patients received four cycles of metronomic paclitaxel (80 mg/m^2 on Days 1, 8, and 15), cyclophosphamide (50 mg/body daily), and capecitabine (1,200 mg/m^2 daily), followed by four cycles of 5-FU (500 mg/m^2), epirubicin (100 mg/m^2), and cyclophosphamide (500 mg/m^2) every 3 weeks. The primary end point was the pathological complete response (pCR) rate.

Results Forty patients formed the intent-to-treat population. The median dose intensities of paclitaxel, cyclophosphamide, and capecitabine were 89.7, 92.1, and 89.8 %, respectively. Five patients discontinued mPCX and two discontinued FEC, primarily because of adverse events, resulting in a per-protocol population (PPS) of 33 patients. The pCR (ypT0/Tis ypN0) rate was 47.5 % (19/40) in the intent-to-treat population and 54.5 % (18/33) in the PPS. The clinical response rates were 36/40 (90.0 %) and 31/33 (93.9 %) in the intent-to-treat and PPS, respectively. The breast conservation rate was 72.7 % (24/33), and 5/13 patients underwent partial resection instead of pre-planned total mastectomy. Grade 3–4 adverse events included neutropenia (35 %), leukopenia (25 %), and hand-foot syndrome (8 %).

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

Electronic supplementary material The online version of this article (doi:10.1007/s00280-014-2492-y) contains supplementary material, which is available to authorized users.

N. Masuda (✉) · M. Mizutani
Department of Surgery, Breast Oncology, National Hospital Organization Osaka National Hospital, 2-1-14 Hoenzaka, Chuo-ku, Osaka 540-0006, Japan
e-mail: nmasuda@alpha.ocn.ne.jp

K. Higaki · S. Ohtani
Hiroshima City Hospital, Hiroshima, Japan

T. Takano
Toranomon Hospital, Tokyo, Japan

N. Matsunami
Osaka Rousai Hospital, Osaka, Japan

T. Morimoto
Yao Municipal Hospital, Osaka, Japan

T. Miyamoto
Gunma Prefectural Cancer Center, Ota, Japan

K. Kuroi
Tokyo Metropolitan Cancer and Infectious Diseases Center, Komagome Hospital, Tokyo, Japan

S. Ohno
Clinical Research Center, National Hospital Organization Kyushu Cancer Center, Fukuoka, Japan

S. Morita
Yokohama City University Medical Center, Kanagawa, Japan

M. Toi
Graduate School of Medicine Kyoto University, Kyoto, Japan

Keywords Triple-negative breast cancer · Metronomic chemotherapy · Weekly paclitaxel · Oral cyclophosphamide · Capecitabine · pCR

Introduction

Triple-negative breast cancer (TNBC) accounts for ~15 % of all breast cancers [1–4]. The prognosis of TNBC is generally favorable in patients with pathological complete response (pCR), but is quite poor in patients with residual invasive tumors [5]. pCR rates in TNBC vary among chemotherapy regimens, adding to the challenge of treating TNBC. For example, anthracycline-based chemotherapy has a pCR rate of 17–27 % [5–8], increasing to 45 % following the addition of a taxane [9]. Sequential therapy with paclitaxel and anthracyclines has achieved a pCR rate of 28 % in TNBC [5].

A typical sequential therapy for TNBC comprises weekly paclitaxel followed by FEC. However, the outcomes of this regimen are unsatisfactory for TNBC, and more effective therapeutic options are needed [10].

The combination of capecitabine and cyclophosphamide appears to be promising, with an all-oral combination giving a response rate of >40 % in metastatic breast cancer, and is both feasible and well tolerated [11, 12]. The addition of capecitabine to a taxane achieved greater efficacy than a taxane/anthracycline combination [13], possibly because of the synergistic effect of increasing PyNPase activity [14, 15]. A combination of low-dose capecitabine and weekly paclitaxel yielded an overall response rate of 46.5 % in metastatic breast cancer [16]. A paclitaxel/cyclophosphamide combination was effective in patients with advanced recurrent breast cancer [17]. Dellapasqua et al. [18] reported that low-dose daily metronomic oral capecitabine and cyclophosphamide (mXC) combined with bevacizumab was effective for treating advanced breast cancer and minimally toxic. These results led to the hypothesis that a combination of paclitaxel, cyclophosphamide, and capecitabine (PCX) is feasible for chemotherapy in breast cancer patients. Two studies [19, 20] have demonstrated that the efficacy and tolerability of paclitaxel administered every week were better than those of paclitaxel administered every 3 weeks. In the first of these reports, the Cancer and Leukemia Group B (CALGB) trial revealed that weekly paclitaxel was associated with a greater response rate, together with a longer time to progression and longer overall survival than administration every 3 weeks. In that study, neutropenia was more common in patients treated every 3 weeks, while neuropathy was more common in patients treated every week. The meta-analysis conducted in the second report [20] confirmed that administration of paclitaxel every week conferred a survival benefit compared with administration every 3 weeks. Weekly paclitaxel was therefore comparable to the concept of metronomic therapy. In the present study, therefore, the promising regimen of the three drugs is referred to as metronomic paclitaxel, cyclophosphamide, and capecitabine (mPCX) [metronomic paclitaxel (80 mg/m^2 on Days 1, 8, and 15), cyclophosphamide (50 mg/body daily), and capecitabine (1,200 mg/m^2 daily), followed by four cycles of 5-FU (500 mg/m^2), epirubicin (100 mg/m^2), and cyclophosphamide (500 mg/m^2) every 3 weeks] and was based on the mCX regimens described above.

Metronomic chemotherapy regimens using combinations of standard drugs that are widely used to treat breast cancer are now being implemented in clinical trials in cancer patients and are proving as effective as maximum therapeutic dose chemotherapeutic regimens but with less toxicity [21–25]. The lower toxicity of these regimens is the main rationale for their adoption [26]. In this study, we examined the histologic effects and safety of four cycles of neoadjuvant mPCX followed by four cycles of neoadjuvant 5-fluorouracil (5-FU)/epirubicin/cyclophosphamide (FEC) in patients with TNBC. Outcomes included tumor response, rate of breast-conserving surgery, and toxicity.

Methods

Patients

Females aged 20–70 years with primary TNBC or HER2-negative breast cancer with low estrogen receptor/progesterone receptor expression (<10 %) were eligible for this study. Exclusion criteria included chemotherapy or hormone therapy for breast cancer in the last 5 years; active double cancer; synchronous bilateral breast cancer; male breast cancer; infection or suspected infection; serious heart disease or history thereof; poorly controlled diabetes mellitus; gastrointestinal ulcer or hemorrhage; or any serious comorbidities or a history of drug allergies that may interfere with treatment. Written informed consent was required to participate in the study. The study protocol was approved by the institutional ethics committees at all study locations, and the procedures followed were in accordance with the ethical standards of these committees and the Helsinki Declaration. This trial was registered on the University Hospital Medical Information Network (identifier: UMIN000003570).

Study design and treatment

This was a multicenter open-label study. Eligible patients received four cycles of mPCX followed by four cycles of FEC (Fig. 1a). Each cycle consisted of 3 weeks with a time

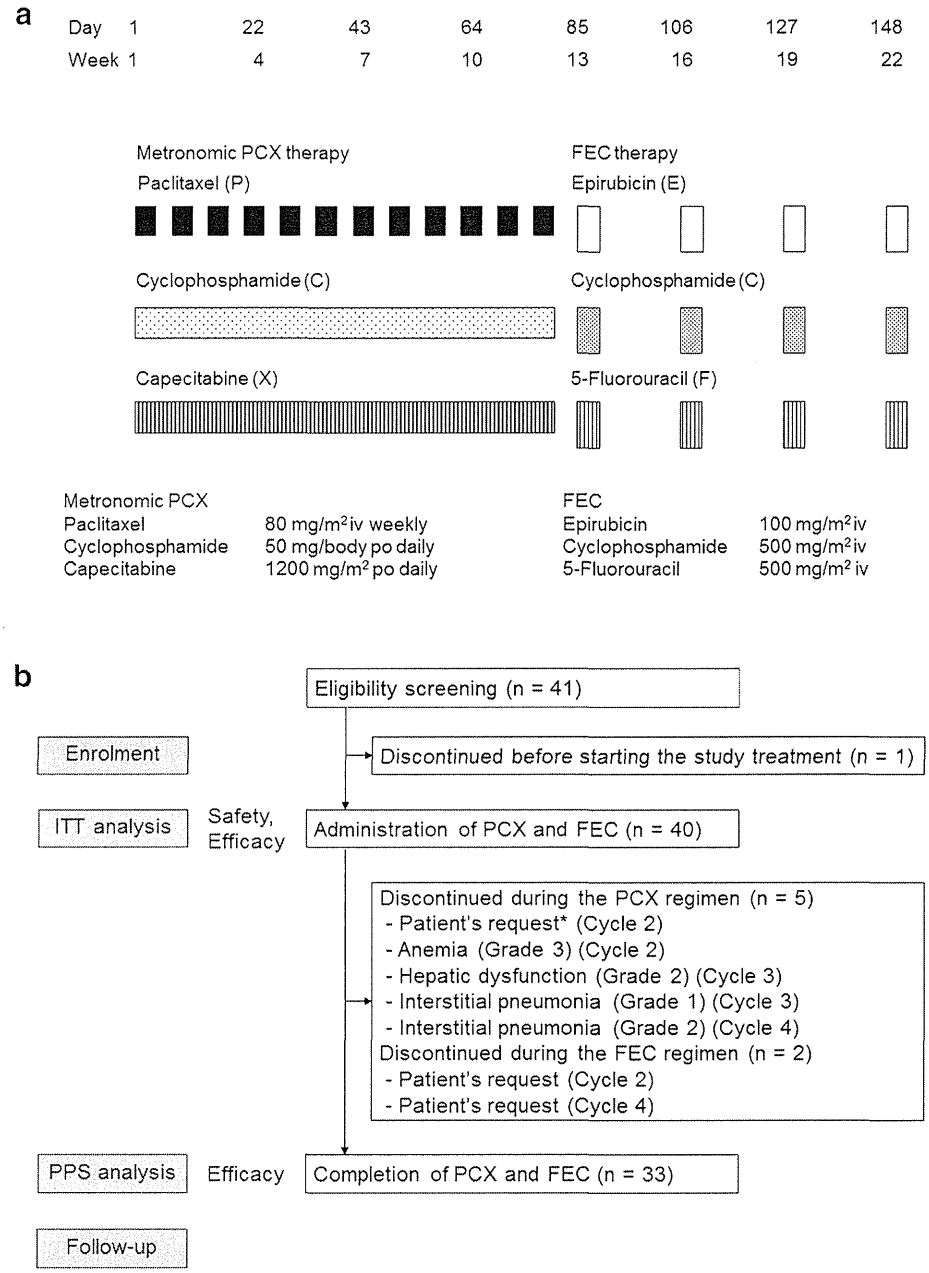


Fig. 1 **a** Study design. During metronomic PCX therapy, patients received intravenous paclitaxel (80 mg/m^2) on Days 1, 8, and 15, oral cyclophosphamide (50 mg) on Days 1–21, and oral capecitabine (1,200 mg/m^2) on Days 1–21 every 3 weeks for four cycles. Patients then received intravenous 5-FU (500 mg/m^2) on Day 1, intravenous epirubicin (100 mg/m^2) on Day 1, and intravenous cyclophosphamide (500 mg/m^2) on Day 1, every 3 weeks for four cycles. **b** Patient disposition. * P-FEC was administered after discontinuation

window of ±3 days, and surgery was performed 3–8 weeks after the last day of the fourth FEC cycle.

The primary efficacy end point was pCR rate. Secondary end points were the rates of breast-conserving surgery and safety findings.

Enrollment started in March 2010. A key concern of the study was to ensure the safety and tolerability of the new regimen. To that end, in March 2011, the efficacy and safety evaluation committee did an interim evaluation on 10 patients initially enrolled, confirming the efficacy and safety of the treatment. The committee members then unanimously voted for continuation of the study based on the results of the interim evaluation.

Assessments

The primary lesion and metastases to lymph nodes were measured within 1 month before treatment initiation, after the second cycle of metronomic mPCX, and after the fourth cycles of mPCX and FEC. The primary end point of pCR was defined as ypT0/Tis and ypN0, namely an absence of invasive cancer in the breast and lymph nodes. Surgical specimens were sectioned into 5-mm-thick slices, and all cut surfaces were examined. pCR in the primary lesion was categorized, as outlined by Kuroi et al. [27] as strict pCR (spCR), pCR with in situ carcinoma (pCRinv), comprehensive pCR (CpCR), near pCR (response very close to that of

SpCR, but with a small number of cancer cells), and quasi-pCR (includes CpCR and near pCR). In the axillary lymph nodes, ITC pN0(i+) of ≤0.2 mm was classified as pN0. A pathologic non-responder was defined as having invasive cancer on pathologic examination (pINV). Adverse events were assessed based on the common terminology criteria for adverse events (CTCAE) version 4.0, except for "nail changes," which were evaluated using the CTCAE version 3.0.

Treatment protocol

The rationales for the choice of paclitaxel [28–35], cyclophosphamide [36], and capecitabine [14–16, 18, 36–39] for metronomic PCX (mPCX) therapy and the appropriate doses [11, 17, 38–41] were determined on the basis of previous clinical studies. Weekly administration of paclitaxel at a dose of 80 mg/m^2 is a standard regimen for breast cancer and was therefore used in this study. For capecitabine, when we converted the doses used in combination regimens [11–13, 16, 18] to daily doses, we found that the dose ranged from 1,000 to 1,670 mg/m^2/day. We decided to use a dose close to the middle of this range of 1,200 mg/m^2 daily (administered as 600 mg/m^2 twice daily). For cyclophosphamide, a daily dose of 50 mg is thought to be safe and effective. Accordingly, the metronomic chemotherapy cycle consisted of paclitaxel (80 mg/m^2 on Days 1, 8, and 15), cyclophosphamide (50 mg once daily), and capecitabine (600 mg/m^2 twice daily) every 3 weeks for 12 weeks.

Metronomic chemotherapy involves administering cytotoxic antineoplastic agents at a low dose, avoiding dose-limiting toxicities by exposing endothelial cells, which proliferate slowly, to continuous low doses of cytotoxic antineoplastic agents.

Because mPCX is a new concept, the criteria for dose reduction and interruption were clearly defined to reduce the incidence of adverse events.

mPCX or the relevant component drug was to be suspended or discontinued in the case of neutrophil count ≤1,000/mm^3 (Grade 3), hand-and-foot syndrome (Grade 2–3), peripheral neuropathy, arthralgia or myalgia (Grade 3) or cystitis (Grade ≥2).

FEC therapy was to be discontinued in the case of Grade 3 neutropenia with fever of ≥38 °C; platelet count <25,000/mm^3 or hemorrhage/platelet transfusion with decreased platelet count; non-hematologic toxicities of ≥Grade 3 (except nausea, vomiting, and anorexia).

The overall safety of the study protocol was assessed after 10 subjects had been enrolled. If >2 subjects were unable to start the second cycle of mPCX therapy within 3 weeks of completing the first because the criteria for starting mPCX or paclitaxel (Online Resource 1) were not met, discontinuation of the study was to be considered.

Sample size and statistical analyses

The sample size was calculated based on a pCR rate of 28 % with preoperative paclitaxel FAC (5-FU/doxorubicin/cyclophosphamide)/FEC therapy and 20 % with an anthracycline-based regimen (FAC/FEC/AC) [5]. Because cyclophosphamide and capecitabine were coadministered with paclitaxel, the expected pCR rate was 40 % at a threshold of 20 %. Under those conditions with $\alpha = 0.05$ and $\beta = 0.2$, 36 evaluable subjects were required, and a sample size of 40 patients was considered sufficient to allow for discontinuations. The proportions of patients with a partial response (PR) or better and of those with a complete response (CR; objective CR), together with 95 % confidence intervals, were calculated from the distribution of the objective response.

Histologic response was measured as the proportion of patients with pCR. For adverse events, the proportions of Grade 1–4 events were calculated. All analyses are presented descriptively as the n (%) of patients or median (range).

Results

Patient characteristics

Forty-one patients were enrolled into the study and 40 (median age 52 years; range 33–69 years) underwent at least one cycle of treatment and were included in the intent-to-treat (ITT) population (Fig. 1b). The median tumor size was 23.7 mm (range 3.5–82 mm) and was classified as N(+) in 40 % (16/40) and weakly positive for ER (i.e., 1–9 %) in 17.5 % (7/40) of patients (Table 1). Five patients withdrew during mPCX at the patient's request in two cases and because of adverse events in three. Two patients withdrew during FEC at their own request. Therefore, the per-protocol population (PPS) consisted of 33 patients (Fig. 1b).

Treatment exposure

Because this regimen was being evaluated for the first time, tolerability was assessed in terms of the relative dose intensity (RDI) of each component, which was classified as RDI in all patient groups (Online Resource 2). The RDI was high in the mPCX phase (paclitaxel 89.7 %; cyclophosphamide 92.1 %; capecitabine 89.8 %) and in the FEC phase (epirubicin 89.8 %).

Table 1 Patient characteristics

Characteristic	Value
N	40
Age, years	
Median (range)	52.0 (33.0, 69.0)
PS	
0	37 (92.5 %)
1	3 (7.5 %)
Tumor stage status	
T1	8 (20.0 %)
T2	27 (67.5 %)
T3	5 (12.5 %)
Tumor size, mm[a]	
Median (range) (mm)	23.7 (3.5, 82.0)
Node status	
N0	24 (60.0 %)
N1	16 (40.0 %)
Disease stage	
Stage I	5 (12.5 %)
Stage IIa	21 (52.5 %)
Stage IIb	10 (25.0 %)
Stage IIIa	4 (10.0 %)
Menopausal status	
Premenopausal	19 (47.5 %)
Postmenopausal	21 (52.5 %)
ER (IHC)	
0 %	33 (82.5 %)
1–9 %	7 (17.5 %)
PgR (IHC)	
0 %	39 (97.5 %)
1–9 %	1 (2.5 %)
HER2 (IHC)	
0	28 (70.0 %)
1	8 (20.0 %)
2	1 (2.5 %)
NA	3 (7.5 %)
Histological grade (B&R classification)	
1	5 (12.5 %)
2	11 (27.5 %)
3	23 (57.5 %)
Unknown	1 (2.5 %)
Sentinel node lymph biopsy before starting the study treatment	
No	36 (90.0 %)
Yes	4 (10.0 %)
n0	4 (100.0 %)
n+	0 (0.0 %)
Surgical treatment planned before starting the study treatment	
BCS	25 (62.5 %)
Mastectomy	15 (37.5 %)

PS performance status, *ER* estrogen receptor, *PgR* progesterone receptor, *HER2* human epidermal growth factor receptor, *IHC* immunohistochemistry, *B&R* Bloom and Richardson grading system, *BCS* breast-conserving surgery

[a] Measured by magnetic resonance imaging or computed tomography; if both were available, the magnetic resonance imaging-determined size was used

Clinical response

The clinical response rate was calculated following an objective evaluation of the clinical response based on palpation and MRI/CT (Table 2). The clinical response rate (based on MRI/CT) was 90.0 % (36/40) in the ITT population and 93.9 % (31/33) in the PPS.

pCR

pCR was achieved after mPCX and FEC by 47.5 % (19/40) of patients in the ITT population and in 54.5 % (18/33) of patients in the PPS. The results for all grades of pCR in both populations are shown in Table 3.

Further analysis on weakly ER-positive patients ($n = 7$) revealed that invasive breast cancer disappeared in four patients (ypT0/Tis) after mPCX-EFC therapy, three of whom were axillary lymph node negative (ypN0). The specific results in these seven patients were SpCR $n0$ ($n = 1$), SpCR $n(+)$ (1), pCRinv n0 (2), near pCR $n(+)$ (2), and non-pCR $n0$ (1).

Relationship between tumor response rates after mPCX and pathological response

Figure 2 shows the tumor response rates in individual patients. Eleven of the 33 patients in the PPS achieved a clinical CR (i.e., a decrease in lesion size of 100 % on MRI/CT). Ten of these 11 patients achieved a pCR (ypT0/Tis ypN0). For the remaining patient, the histological rating for the primary focus was SpCR (no residual invasive or non-invasive tumor); however, this patient was positive for lymph node invasion.

Surgical procedures

Breast-conserving surgery was planned in 25 patients in the ITT population (including 20 in the PPS), and the breast was successfully conserved after surgery in 23 patients (19 from the PPS), corresponding to a success rate of 92.0 (95 % CI: 81.4–100.0 %; 95 % success rate and 95 % CI: 85.4–104.6 % in the PPS). The other two patients underwent total mastectomy.

In 15 patients in the ITT population (including 13 in the PPS), total mastectomy was planned, but breast-conserving surgery (BCS) was possible in six patients (40 %, 95 % CI: 15.2–64.8 %; BCS was possible in five (38.5 %) of the 13 patients in the PPS (95 % CI: 12.0–64.9 %)). The other nine patients (eight from the PPS) underwent total mastectomy, as planned. Therefore, the overall rate of breast conservation in the ITT was 72.5 % (29/40, 95 % CI: 58.7–86.3 %). The rate in the PPS was 72.7 % (24/33; 95 % CI: 57.5–87.9 %).

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

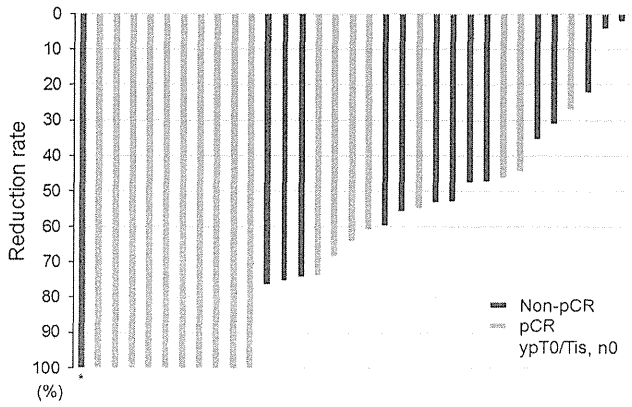


Fig. 2 Tumor response rates. Reduction in lesion size from baseline (%) to the time of mPCX therapy completion in individual patients. *This patient achieved ypT0/Tis in the breast, but an invasive tumor was found in the axillary lymph node. *pCR* pathologic complete response

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 ≥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 ≥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.

Acknowledgments The present study was funded by the Japan Breast Cancer Research Group. We thank Marion Barnett and Daniel McGowan, PhD, for providing editorial support. The authors would also like to gratefully acknowledge the support of the patients and staff at each institute, management office, and data center.

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.

References

1. Iwase H, Kurebayashi J, Tsuda H et al (2010) Clinicopathological analyses of triple negative breast cancer using surveillance data from the Registration Committee of the Japanese Breast Cancer Society. Breast Cancer 17:118–124
2. Japanese Breast Cancer Society (2004) Investigative Report on Registration of Breast Cancer Patients in Japan [in Japanese]. No. 35
3. Kang SP, Martel M, Harris LN (2008) Triple negative breast cancer: current understanding of biology and treatment options. Curr Opin Obstet Gynecol 20:40–46
4. Bauer KR, Brown M, Cress RD et al (2007) Descriptive analysis of estrogen receptor (ER)-negative, progesterone receptor (PR)-negative, and HER2-negative invasive breast cancer, the so-called triple-negative phenotype: a population-based study from the California Cancer Registry. Cancer 109:1721–1728
5. Liedtke C, Maouni D, Hoss KR et al (2008) Response to neoadjuvant therapy and long term survival in patients with triple-negative breast cancer. J Clin Oncol 26:1275–1281
6. Bidard FC, Matthieu MC, Chollet P et al (2008) p53 status and efficacy of primary anthracyclines/alkylating agent-based regimen according to breast cancer molecular classes. Ann Oncol 19:1261–1265
7. Carey LA, Dees EC, Sawyer L et al (2007) The triple negative paradox: primary tumor chemosensitivity of breast cancer subtypes. Clin Cancer Res 13:2329–2334
8. Keam B, Im SA, Kim HJ et al (2007) Prognostic impact of clinicopathologic parameters in stage II/III breast cancer treated with neoadjuvant docetaxel and doxorubicin chemotherapy: paradoxical features of the triple negative breast cancer. BMC Cancer 7:203
9. Rouzier R, Perou CM, Symmans WF et al (2005) Breast cancer molecular subtypes respond differently to preoperative chemotherapy. Clin Cancer Res 11:5678–5685
10. Cleator S, Heller W, Coombes RC (2007) Triple-negative breast cancer; therapeutic options. Lancet Oncol 8:235–244
11. Ohno S, Mitsuyama S, Tamura K et al (2007) Dose of capecitabine and cyclophosphamide combination therapy in patients with metastatic breast cancer. Anticancer Res 27:1009–1013

12. Yoshimoto M, Takao S, Hirata M et al (2012) Metronomic oral combination chemotherapy with capecitabine and cyclophosphamide: a phase II study in patients with HER2-negative metastatic breast cancer. Cancer Chemother Pharmacol 70:331–338
13. O'Shaughnessy J, Miles D, Vukelja S et al (2002) Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: phase III trial results. J Clin Oncol 20:2812–2823
14. Sawada N, Fujimoto-Ouchi K, Ishikawa T et al (2002) Antitumor activity of combination therapy with capecitabine plus vinorelbine, and capecitabine plus gemcitabine in human tumor xenograft models. Proc Am Assoc Cancer Res 43:1088 (abstract #5388)
15. Endo M, Shinbori N, Fukase Y et al (1999) Induction of thymidine phosphorylase expression and enhancement of efficacy by cyclophosphamide in mammary tumor models. Int J Cancer 83:127–134
16. Taguchi T, Yamamoto D, Masuda N et al (2013) Low dose capecitabine plus weekly paclitaxel in patients with metastatic breast cancer: a multicenter phase II study KBCSG-0609. Cancer Chemother Pharmacol 71:741–747
17. Masuda N, Nakayama T, Yamamura J et al (2010) Phase I study of combination therapy with weekly paclitaxel and cyclophosphamide for advanced recurrent breast cancer. Cancer Chemother Pharmacol 66:89–94
18. Dellapasqua S, Bertolini F, Bagnardi V et al (2008) Metronomic cyclophosphamide and capecitabine combined with bevacizumab in advanced breast cancer. J Clin Oncol 26:4899–4905
19. Seidman AD, Berry D, Cirrincione C et al (2008) Randomized phase III trial of weekly compared with every-3-weeks paclitaxel for metastatic breast cancer, with trastuzumab for all HER-2 overexpressors and random assignment to trastuzumab or not in HER-2 nonoverexpressors: final results of Cancer and Leukemia Group B protocol 9840. J Clin Oncol 26:1642–1649
20. Mauri D, Kamposioras K, Tsali L et al (2010) Overall survival benefit for weekly versus three-weekly taxanes regimens in advanced breast cancer: a meta-analysis. Cancer Treat Rev 36:69–74
21. Walker P (2013) Phase II trial of neoadjuvant metronomic chemotherapy in triple-negative breast cancer (protocol ID: LJCC 07-03, NCT00542191), http://www.cancer.gov/search/ViewClinicalTrials.aspx?cdrid=573471&protocolsearchid=5968740&version=healthprofessional. Accessed 2 Oct 2013
22. Glode LM, Barqawi A, Crighton F et al (2003) Metronomic therapy with cyclophosphamide and dexamethasone for prostate carcinoma. Cancer 98:1643–1648
23. Emmenegger U, Man S, Shaked Y et al (2004) A comparative analysis of low-dose metronomic cyclophosphamide reveals absent or low-grade toxicity on tissues highly sensitive to the toxic effects of maximum tolerated dose regimens. Cancer Res 64:3994–4000
24. Colleoni M, Orlando L, Sanna G et al (2006) Metronomic low-dose oral cyclophosphamide and methotrexate plus or minus thalidomide in metastatic breast cancer: antitumor activity and biological effects. Ann Oncol 17:232–238
25. Bottini A, Generali D, Brizzi MP et al (2006) Randomized phase II trial of letrozole and letrozole plus low-dose metronomic oral cyclophosphamide as primary systemic treatment in elderly breast cancer patients. J Clin Oncol 24:3623–3628
26. Kerbel RS (2011) Reappraising antiangiogenic therapy for breast cancer. Breast 20:S56–S60
27. Kuroi K, Toi M, Tsuda H et al (2006) Issues in the assessment of the pathologic effect of primary systemic therapy for breast cancer. Breast Cancer 13:38–48
28. Kimura M, Sano M, Hujimori M et al (2008) Neoadjuvant paclitaxel for operable breast cancer: multicenter phase II trial with clinical outcomes. Anticancer Res 28:1239–1244
29. Belotti D, Vergani V, Drudis T et al (1996) The microtubule-affecting drug paclitaxel has antiangiogenic activity. Clin Cancer Res 2:1843–1849
30. Milross CG, Mason KA, Hunter NR et al (1996) Relationship of mitotic arrest and apoptosis to antitumor effect of paclitaxel. J Natl Cancer Inst 88:1308–1314
31. Symmans WF, Volm MD, Shapiro RL et al (2000) Paclitaxel-induced apoptosis and mitotic arrest assessed by serial fine-needle aspiration: implications for early prediction of breast cancer response to neoadjuvant chemotherapy. Clin Cancer Res 6:4610–4617
32. Griffon-Etienne G, Boucher Y, Brekken C et al (1999) Taxane-induced apoptosis decompresses blood vessels and lowers interstitial fluid pressure in solid tumors: clinical implications. Cancer Res 59:3776–3782
33. Milas L, Hunter NR, Mason KA et al (1995) Role of reoxygenation in induction of enhancement of tumor radioresponse by paclitaxel. Cancer Res 55:3564–3568
34. Green MC, Buzdar AU, Smith T et al (2005) Weekly paclitaxel improves pathologic complete remission in operable breast cancer when compared with paclitaxel once every 3 weeks. J Clin Oncol 23:5983–5992
35. Loesch DM, Greco F, O'Shaughnessy J et al (2007) A randomized multicenter phase III trial comparing doxorubicin + cyclophosphamide followed by paclitaxel or doxorubicin + paclitaxel followed by weekly paclitaxel as adjuvant therapy for high breast cancer. J Clin Oncol 25(suppl 18):517
36. Ellis GK, Barlow WE, Russell CA et al (2006) SWOG 0012, a randomized phase III comparison of standard doxorubicin and cyclophosphamide followed by weekly paclitaxel versus weekly doxorubicin and daily oral cyclophosphamide plus G-CSF followed by weekly paclitaxel as neoadjuvant therapy for inflammatory and locally advanced breast cancer. Proc Am Soc Clin Oncol 24(suppl 18):537
37. Bari M, D'Andrea MR, Azzarello G et al (2005) Salvage therapy with capecitabine plus weekly paclitaxel in heavily pretreated advanced breast cancer. A multicenter phase II study. Am J Cancer 4:307–313
38. Blum JL, Dees EC, Chacko A et al (2006) Phase II trial of capecitabine and weekly paclitaxel as first-line therapy for metastatic breast cancer. J Clin Oncol 24:4384–4390
39. Blum JL, Dees EC, Vukelja SJ et al (2007) Phase II trial of capecitabine and weekly paclitaxel in patients with metastatic breast cancer previously treated with every-3-week taxane therapy. Clin Breast Cancer 7:465–470
40. Nakayama T, Masuda M, Kamigaki S et al (2008) Phase I clinical study of weekly paclitaxel and cyclophosphamide combination therapy for advanced and recurrent breast cancer [in Japanese]. Jpn Soc Clin Oncol 43:508 (abstract OS064-6)
41. Findlay MPN, Riley GA, Ackland S et al (2002) Capecitabine and oral cyclophosphamide: A novel oral treatment combination for advanced cancer. Ann Oncol 13:24 (abstract 86P)
42. Kerbel RS, Klement G, Pritchard KI, Kamen B (2012) Continuous low-dose anti-angiogenic/metronomic chemotherapy: from the research laboratory into the oncology clinic. Ann Oncol 13:12–15
43. Lien K, Georgsdottir S, Sivanathan L, Chan K, Emmenegger U (2013) Low-dose metronomic chemotherapy: a systematic literature analysis. Eur J Cancer 49:3387–3395
44. Bear HD, Anderson S, Smith R et al (2006) Sequential preoperative or postoperative docetaxel added to preoperative doxorubicin plus cyclophosphamide for operable breast cancer: national Surgical Adjuvant Breast and Bowel Project B-27. J Clin Oncol 24:2017–2019
45. von Minckwitz G, Schneeweiss A, Salat C et al (2013) A randomized phase II trial investigating the addition of carboplatin to neoadjuvant therapy for triple-negative and HER2-positive

early breast cancer (GeparSixto). In: 49th ASCO annual meeting (meeting abstract): 1004, Chicago, IL
46. Sikov WM, Berry DA, Perou CM et al (2013) Impact of the addition of carboplatin and/or bevacizumab to neoadjuvant weekly paclitaxel followed by dose-dense AC on pathologic complete response (pCR) rates in triple-negative breast cancer (TNBC): CALGB 40603 (Alliance). In: 36th annual SABCS (meeting abstract): S5-01, San Antonio, TX
47. von Minckwitz G, Eidtmann H, Rezai M et al (2012) Neoadjuvant chemotherapy and bevacizumab for HER2-negative breast cancer. N Engl J Med 366:299–309