床試験科で行う、という点が一番大変だったと思います。

医師主導治験の場合、IRB 事務局業務の専任スタッフが必要だと思いました。

（審査資料の作成、調整事務局とのやり取りなど）

（埼玉県立がんセンター）

正規職員としての CRC を持たない当センターの問題であるが，研究費を，人件費として使用できなかった。そのために，患者の来院日を限定しなくてはならなかった。Paclitaxel 80 mg/m²/週 1 回 x 12 コース + Carboplatin AUC5/3 週 1 回 x 4 コースで，好中球減少によりプロトコール規定で治療継続ができなかった症例がいた。

（四国がんセンター）

今回医師主導型治験として本試験を行うにあたり、試験施行に関する手続きは複雑なものであったが、医師主導型治験の担当を置くことにより対処できた。CRC 以外にも、事務関係の迅速な対応も得られ、継続的な医師主導型治験を行う体制ができた。

さらに、当院では同一期間中に重篤な有害事象は 2 件に認められ、治験調整事務局へ報告を行い、当該施設以外の治験参加施設への周知を適切に行うことが可能であった。治験実施にあたり、CRC の絶大な協力を得ることができ、ほぼ順調に遂行できていると考えられた。

E．結論

（埼玉県立がんセンター）

初めての，医師主導試験出あるために，手順書からの作成となり，最後の参加となってしまったが，今後同様の試験に参加した場合には，もう少し円滑に実施できると思う。

（四国がんセンター）

治験実施にあたり、CRC、事務担当者の絶大な協力を得ることができ、ほぼ順調に遂行できたと考えられた。

本試験は、諸部門の協力の元、円滑に遂行できた。本院における医師主導型治験を行う体制作りは完了し、実施のためのノウハウを蓄積することができた。

G．研究発表

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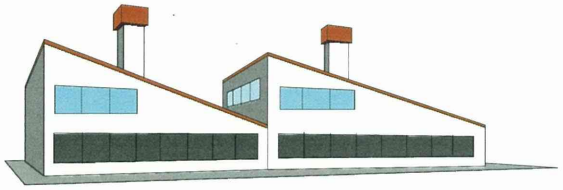
F．知的財産の出願・登録状況

該当なし。

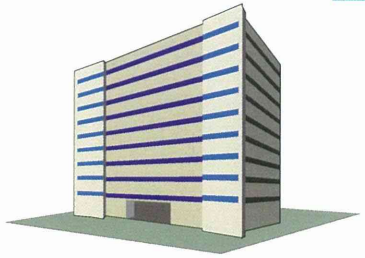
別添１）

研究実施体制

オペレーション部門



治験薬提供者
（ブリストル・マイヤーズ
株式会社）
・治験薬・安全性情報の提供



国立がんセンター
- 治験調整事務局
- 治験薬発送
- 治験届の手続き
- 副作用情報取り扱い

北里研究所
・データマネージ
メント

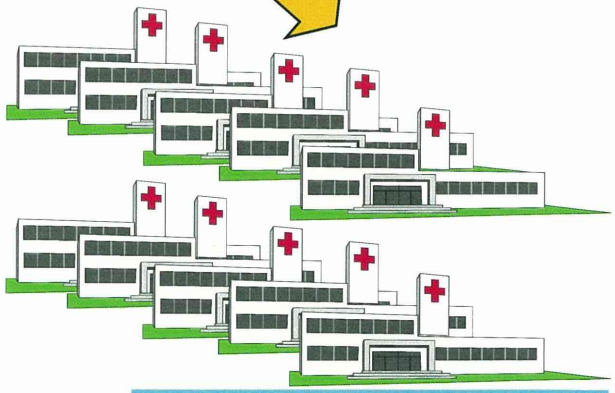
治験支援サイト

モニタリング担当者
（日揮ファーマサービス）

病理診断
パネル（3名）

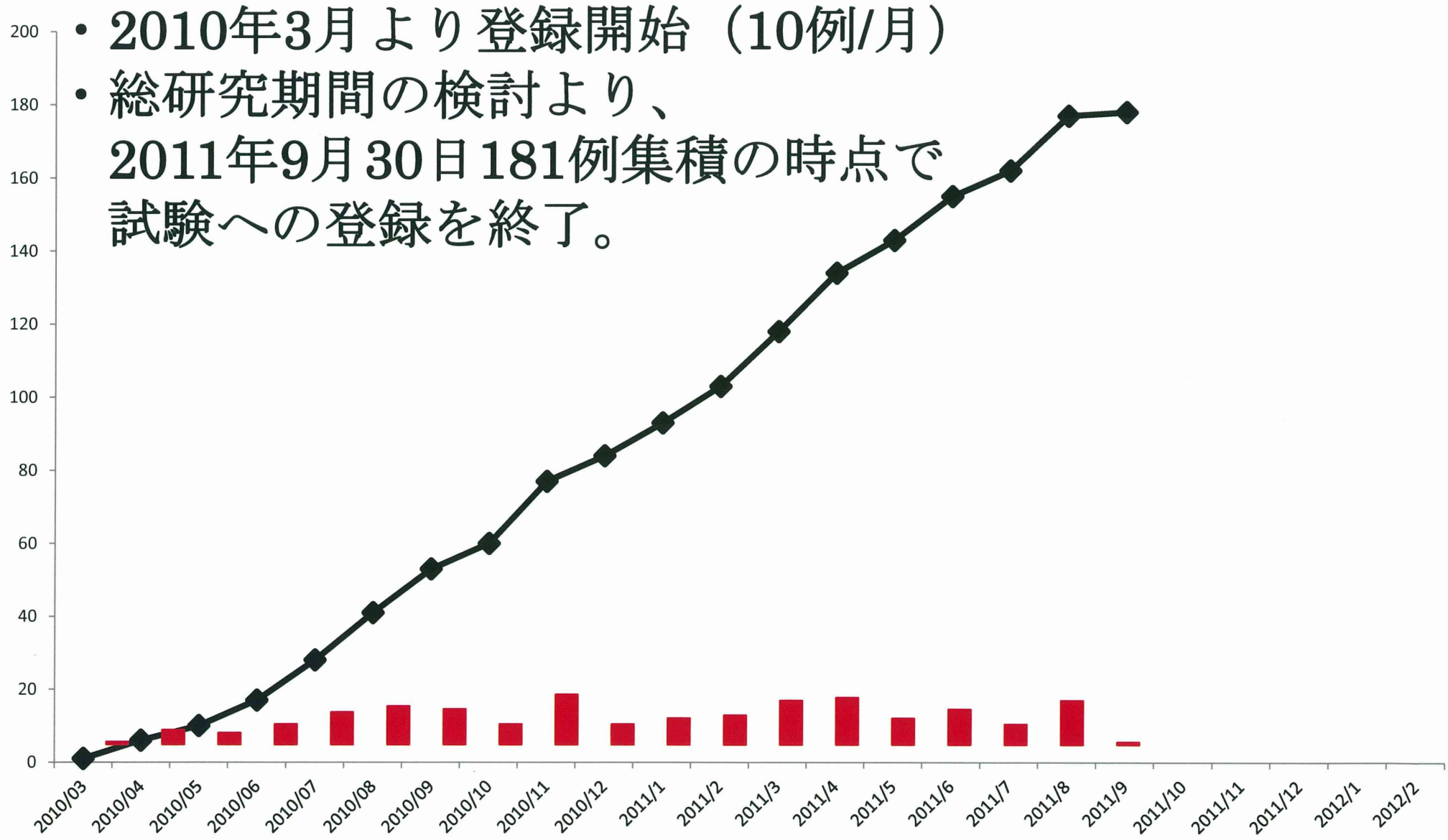
効果・安全性
評価委員会（3名）

監査担当
（MICメディカル）



治験実施施設
(10施設)

別添 2)　本試験への症例登録状況



別添 3)

患者背景

	CP群 (N=88)	P群 (N=93)
年齢		
50歳未満	60.3%	57%
50歳以上	39.7%	43%
臨床病期		
II	80.7%	80.6%
IIIA	19.3%	19.4%
ホルモン受容体陽性	55.7%	59.1%

別添 4)

病理中央診断結果

（2011年9月16日、12月8日、2012年3月23日実施138例分）

	CP群 (N=67)	P群 (N=71)
pCR	19	14
pCR率	28.4%	19.7%
Non-pCR	48	57

別添 5)

各治療群におけるgrade 3以上の有害事象 (2012年03月の時点)

事象名	CP群 (N=88)	(CEF投与中)	P群 (N=93)	(CEF投与中)
好中球数減少	101	(25)	46	(35)
発熱性好中球減少	19	(15)	14	(14)
貧血	14	(1)	1	(1)
血小板数減少	1	-	0	-
Transaminase上昇	3	-	4	(1)
悪心・嘔吐	3	(1)	2	(2)
感染症	4	(2)	1	(1)
失神	2	(1)	0	-
末梢性感覚ニューロパチー	2	-	1	-
粘膜炎	1	(1)	1	(1)
疲労	1	-	1	(1)

III 研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表レイアウト

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Nakamura S, Ando M, Masuda N, Aogi K, Ino H, Iwata H, Tokuda Y, Yamamoto N, Kasai H, Takeuchi M, Tsuda H, Akiyama F, Kurosumi M, Fujiwara Y	Randomized Phase II study of primary systemic chemotherapy and trastuzumab for operable HER2 positive breast cancer	Clinical Breast Cancer	12	49-56	2012

IV 研究成果の刊行物・別刷

Original Study

Randomized Phase II Study of Primary Systemic Chemotherapy and Trastuzumab for Operable HER2 Positive Breast Cancer

Seigo Nakamura,[1,2] Masashi Ando,[3] Norikazu Masuda,[4] Kenjiro Aogi,[5] Hiroyo Ino,[6] Hiroji Iwata,[7] Yutaka Tokuda,[8] Naohito Yamamoto,[9] Hiroi Kasai,[3] Masahiko Takeuchi,[10] Hitoshi Tsuda,[3] Futoshi Akiyama,[11] Masafumi Kurosumi,[12] Yasuhiro Fujiwara[3]

Abstract

Primary systemic therapy for patients with HER2$^+$(human epidermal growth factor receptor 2 positive) breast cancer may be improved by adding trastuzumab to chemotherapy. This randomized phase II trial compared 2 chemotherapy regimens comprising FEC (5-fluorouracil/epirubicin/cyclophosphamide), trastuzumab and either PH (paclitaxel) or DH (docetaxel) in 102 patients. FEC-PH and FEC-DH achieved high pathologic complete response rates. Breast conserving surgery was possible in more patients in the paclitaxel arm.

Background: In primary systemic therapy in patients with human epidermal growth factor receptor 2 positive (HER2$^+$) breast cancer, improvements in pathologic complete response (pCR) rate have been achieved by administering trastuzumab. **Patients and Methods:** Patients with stage II or IIIA HER2$^+$ operable breast cancer were randomly assigned to receive four 3-weekly cycles of FEC (5-fluorouracil 500 mg/m^2, epirubicin 100 mg/m^2, cyclophosphamide 500 mg/m^2) followed by 4 cycles of 3-weekly trastuzumab (8 mg/kg week 1 and then 6 mg/kg) with either 12 weekly doses of paclitaxel 80 mg/m^2 (FEC-PH) or 4 cycles of 3-weekly docetaxel 75 mg/m^2 (FEC-DH). **Results:** Between March 2007 and June 2008, 102 patients were enrolled. Forty-nine patients receiving FEC-PH and 47 receiving FEC-DH were assessable for efficacy and safety. Eighty-four patients completed treatment and underwent surgery. There was no significant difference in the pCR rate between the 2 groups (46.9% [95% CI, 33.7%-60.6%] with FEC-PH vs. 42.6% [95% CI, 29.5%-56.8%] with FEC-DH; $P = .67$). Analysis by hormone receptor (HR) status showed pCR rates of 54.2% (32/59) in HR$^-$ tumors and 29.7% (11/37) in HR$^+$ tumors ($P = .02$). Among HR$^-$ tumors, the pCR rates were 65.4% and 45.5% in patients treated with FEC-PH and FEC-DH, respectively ($P = .13$). **Conclusions:** There was no significant difference in pCR rate between FEC-PH and FEC-DH. Both regimens achieved higher pCR rates in HR$^-$ than HR$^+$ breast cancer, and there was a trend toward higher pCR in HR$^-$ tumors with FEC-PH compared with FEC-DH. Further investigation is warranted to explore the relationship between efficacy and HR status.

Clinical Breast Cancer, Vol. 12, No. 1, 49-56
Keywords: Breast cancer, HER2, Primary systemic therapy, Trastuzumab

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Submitted: Jul 11, 2011; Revised: Oct 12, 2011; Accepted: Oct 17, 2011

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1526-8209/$ - see frontmatter
doi: 10.1016/j.clbc.2011.10.002

Introduction

Primary systemic therapy (PST) is regarded as one of the standard therapies for locally advanced breast cancer and selected patients with operable disease to facilitate breast conservation.[1–4] Patients achieving pathologic complete response (pCR) in the primary lesion and with no residual tumor in axillary nodes after PST have longer recurrence-free survival than those without pCR.[4–6] Consequently, pCR is commonly used as a surrogate for long-term outcome when evaluating novel chemotherapy regimens. Currently, sequential regimens, including an anthracycline followed by either weekly paclitaxel or 3-weekly docetaxel are commonly used to achieve high pCR rates.[3,7]

Trastuzumab plays an important role in therapy for human epidermal growth factor receptor 2 (HER2) positive ($HER2^+$) breast cancer, and its efficacy has been proven in both the adjuvant[8-10] and the metastatic[11,12] settings. In the neoadjuvant setting, improvements in the pCR rate have been achieved by administering trastuzumab with PST in patients with $HER2^+$ breast cancer. In a randomized trial that compared chemotherapy with or without trastuzumab, the trastuzumab-containing regimen improved the pCR rate (65.2% vs. 26.3%; $P = .002$).[13] A second randomized trial, the neoadjuvant herceptin (NOAH), showed a higher pCR rate with the combination of chemotherapy and trastuzumab than chemotherapy alone (39% vs. 20%; $P = .002$).[14] In addition, single-arm trials that evaluated the combination of chemotherapy and trastuzumab as PST showed high pCR rates.[15–20] Recently, it was reported that patients who achieve pCR have longer survival compared with those who do not achieve pCR, even in a $HER2^+$ population.[21,22] It is possible, therefore, that pCR could be considered to be a surrogate marker for the efficacy of PST, even in patients with $HER2^+$ breast cancer, although definitive evidence is required to confirm this proposition. Based on these data, we conducted a randomized phase II trial to compare pCR rates achieved with FEC (5-fluorouracil/epirubicin/cyclophosphamide) followed by weekly paclitaxel plus trastuzumab and FEC followed by 3-weekly docetaxel plus trastuzumab as PST for $HER2^+$ breast cancer.

Patients and Methods

Patient Eligibility

Eligible patients had previously untreated, unilateral, histologically confirmed, invasive, noninflammatory breast carcinoma. Histologic confirmation of invasive cancer was performed by core needle biopsy (CNB). $HER2^+$ was defined as a score of 3+ by immunohistochemistry or a HER2 gene copy-chromosome 17 ratio of ≥ 2.0 by fluorescence in situ hybridization. Patients with a tumor ≥ 2 cm at the largest dimension by ultrasonography or <2 cm with axillary lymph node metastasis clinically diagnosed as positive were eligible (clinical stage II and IIIA). Patients with axillary nodes enlarged by >1 cm at the largest dimension according to ultrasonography were considered node positive without the need for confirmatory biopsy. Patients with T4N3 (supraclavicular lymph node), or distant metastatic disease (M1) were excluded from the study.

Other requirements were age between 18 and 65 years, ECOG (Eastern Cooperative Oncology Group) performance status 0 to 2, adequate bone marrow function (absolute granulocyte count $\geq 1500/mm^3$ and platelet count $\geq 100,000/mm^3$), liver function (total bilirubin level ≤ 1.5 mg/dL and liver transaminase levels [aspartate aminotransferase and alanine aminotransferase] ≤ 60 IU/L), and renal function (serum creatinine level ≤ 1.5 mg/dL). Patients with a history of ischemic cardiac disease and cardiomyopathy or a left ventricular ejection fraction (LVEF) $<60\%$ according to echocardiogram were excluded. Patients with clinically negative axillary lymph nodes had the option of undergoing pretreatment sentinel lymph node biopsy (SLNB). The study was approved by institutional review boards and was conducted in accordance with the Declaration of Helsinki. All the patients provided written informed consent.

Study Design and Preoperative Systemic Therapy

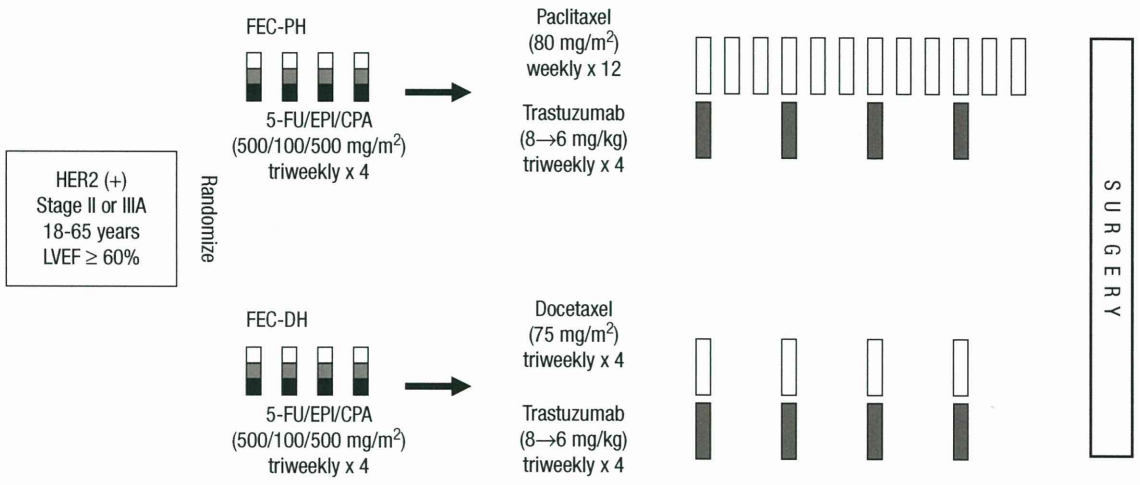
Patients were randomly assigned to receive either FEC followed by the combination of paclitaxel and trastuzumab (FEC-PH) or FEC followed by the combination of docetaxel and trastuzumab (FEC-DH). The dose and schedule of FEC and docetaxel were selected based on efficacy and safety data from our previously reported study of PST.[23,24] FEC consisted of 5-fluorouracil 500 mg/m^2, epirubicin 100 mg/m^2, and cyclophosphamide 500 mg/m^2 administered by intravenous (I.V.) infusion on day 1 every 3 weeks for 4 cycles (Figure 1). Paclitaxel was administered at 80 mg/m^2 I.V. over 1 hour on days 1, 8, and 15 every 3 weeks for 4 cycles. Docetaxel was administered at 75 mg/m^2 I.V. over 1 hour on day 1 every 3 weeks for 4 cycles. In both arms, trastuzumab was administered at a dose of 8 mg/kg I.V. over 90 minutes on day 1 of the first cycle and subsequent doses were administered at a dose of 6 mg/kg over 30 minutes every 3 weeks for a total of 4 cycles.

If a patient developed grade ≥ 3 febrile neutropenia, thrombocytopenia $<25,000/mm^3$, or grade ≥ 3 nonhematologic toxicity, then the doses of epirubicin and docetaxel were reduced by 25% and 20%, respectively, in subsequent cycles. The dose of paclitaxel was reduced by 25% in subsequent cycles if a patient developed grade 3 neurotoxicity. Before administration of the following cycle of FEC or docetaxel, the patients were required to have a granulocyte count $\geq 1500/mm^3$, platelet count $\geq 75,000/mm^3$, and no nonhematologic toxicity of grade >2 (excluding alopecia). Before administration of the next cycle of paclitaxel, the patients were required to have a granulocyte count $\geq 1000/mm^3$, platelet count $\geq 75,000/mm^3$, and no nonhematologic toxicity of grade >2 (excluding alopecia). If toxicity did not improve within 2 weeks, then chemotherapy and trastuzumab were discontinued and surgery was recommended.

Therapy After Preoperative Chemotherapy

Patients who were considered candidates for breast-conserving therapy (BCT) were offered lumpectomy. Patients who refused or were considered inappropriate for BCT received total mastectomy. Axillary lymph node dissection (AxLND) was mandatory, except in the patients diagnosed with nonmetastatic disease by SLNB before PST. Surgery was performed within 8 weeks after completion of preoperative chemotherapy. All the patients who underwent BCT received whole-breast irradiation. After completion of preoperative chemotherapy and surgery, the patients with hormone receptor (HR) positive (HR^+) disease received adjuvant endocrine therapy. After completion of local therapy, adjuvant trastuzumab was administered every 3 weeks for up to 1 year. The patients with HR^+ breast cancer received adjuvant trastuzumab in combination with endocrine therapy.

Figure 1 Study Regimen



Study Evaluation and Criteria

The HER2 status of a CNB was determined by immunohistochemistry and/or fluorescence in situ hybridization performed in each institution (no central review) before study enrollment. After completion of PST, resected specimens and CNB specimens were evaluated centrally by 3 breast pathologists (H.T., F.A. and M.K.). The pCR was defined as the absence of viable invasive tumor in both the breast and the axillary nodes. Patients with residual ductal carcinoma in situ (DCIS) in breast tissue and no viable invasive tumor in the axillary nodes also were classified as having pCR. Clinical response was evaluated by palpation after each cycle by using the response evaluation criteria in solid tumors.[25]

All adverse events were evaluated according to the CTCAE (Common Terminology Criteria for Adverse Events) v3.0.[26] Infusion reactions were defined by the occurrence of the following symptoms during infusion or within 24 hours after starting trastuzumab: pyrexia, chills, nausea, vomiting, pain, headache, cough, dyspnea, dizziness, rash, pruritus, general malaise, skin eruption, and decrease in blood pressure.

Endpoints and Statistical Analysis

The primary endpoint was the pCR rate. The secondary endpoints were disease-free survival, clinical response rate, breast conservation rate, and safety. In this report, disease-free survival is not reported because of the short follow-up. Analyses of efficacy and safety were performed in the intent-to-treat (ITT) population. The ITT population comprised subjects fulfilling the study inclusion criteria who had received at least one dose of study chemotherapy. The per-protocol population comprised ITT subjects who had undergone surgery in this study without serious violations of the inclusion criteria. As sensitivity analysis, the pCR rates among the per-protocol population were calculated. By assuming a difference in the pCR rate between the 2 groups of 10% and an expected baseline pCR rate of 30%, a sample size of 49 patients in each treatment group was necessary to demonstrate a higher pCR rate with a probability of 85%. The target number of patients was considered to be 100 patients to allow for patient dropout. The pCR was compared between 2 groups by using the χ^2 test. P values $<.05$ were considered statistically significant.

Results

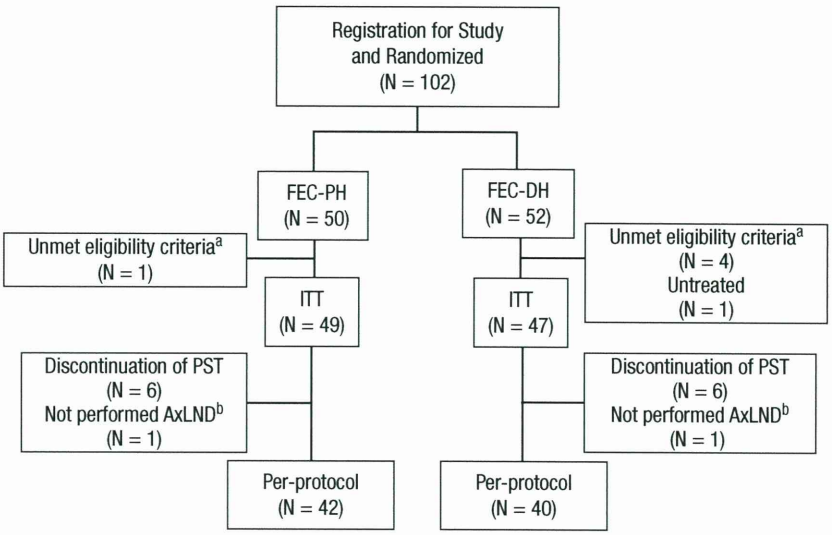
Patient Characteristics

Between March 2007 and June 2008, 102 patients were enrolled in this study. Of these, 49 patients receiving FEC-PH and 47 receiving FEC-DH were evaluable in the ITT population. According to central review, 4 patients were considered ineligible (2 patients not $HER2^+$, 1 not evaluable for HER2 status, 1 with noninvasive carcinoma in the CNB specimen). One patient had an aneurysm of the thoracic aorta immediately after the first cycle of FEC, discontinued FEC, and, therefore, was considered ineligible. One patient did not receive PST because of persistent hypertension (Figure 2).

The characteristics of the ITT population are shown in Table 1. Distribution of tumor size was similar in the 2 treatment groups. The proportion of patients with clinically diagnosed axillary node-positive tumors was higher in the FEC-DH arm. Approximately two-thirds of patients had HR^- tumors, with a slightly higher representation in the FEC-DH than in the FEC-PH arm.

One patient in the FEC-DH arm was considered not evaluable for pathologic response by central review because she had not undergone AxLND or SNLB before PST and had DCIS in the breast after surgery. Eighty-four patients received surgery after completion of PST. The HR and HER2 status of the breast tumors were not reassessed after surgery. Twelve of 72 patients who received AxLND had lymph-node metastases. Two patients did not undergo either AxLND or SLNB before PST. Therefore, 82

Figure 2 Consort Diagram



[a]Three Cases Were Human Epidermal Growth Factor Receptor 2 Negative (HER2$^-$) by Central Review. [b]Axillary Node Dissection.

patients (42 in the FEC-PH arm and 40 in the FEC-DH arm) were evaluated in the per-protocol population (Figure 2).

Treatment Exposure

Ninety-one (94.8%) of 96 patients completed 4 cycles of FEC. Four patients discontinued FEC due to adverse events, and one patient discontinued due to disease progression after 2 cycles of FEC. Among patients who completed 4 cycles of FEC, 3 discontinued PH (grade 3 neurotoxicity in 2 patients; suicide in 1 patient) and 4 discontinued DH (adverse events in 2 patients; disease progression after 1 cycle in 1 patient; refusal in one patient). Thus, 43 of 49 patients (87.8%) in the FEC-PH arm and 41 (87.2%) of 47 patients in the FEC-DH arm completed PST.

Efficacy

In the ITT population, 23 (46.9%) of 49 patients receiving FEC-PH and 21 (44.7%) of 47 patients receiving FEC-DH achieved a pCR according to central pathologic review. The difference between FEC-PH and FEC-DH is 2.3% (95% confidence interval [CI], −17.7% to 22.2%; $P = .82$). The pCR rates were 54.8% with FEC-PH and 50.0% with FEC-DH in the per-protocol population. The difference is 4.8% (95% CI, −16.8% to 26.4%; $P = .67$). The difference between the 2 arms were <10%. The pCR rate included 24 patients with DCIS in the breast (10 in the FEC-PH arm and 14 in the FEC-DH arm). No patients with pCR in the breast had persistent nodal carcinoma. The pCR rates according to institutional review were 44.9% (22/49) in the FEC-PH arm and 36.2% (17/47) in the FEC-DH arm; 4 patients who were diagnosed with residual invasive carcinoma in the breast by institutional review were assessed as pCR with DCIS by central review.

Subpopulation analysis according to HR status showed pCR rates of 54.2% (32/59) in HR$^-$ tumors and 29.7% (11/37) in HR$^+$ tumors ($P = .02$). The pCR rates in patients with HR$^+$ tumors were 26.1% with FEC-PH and 35.7% with FEC-DH ($P = .54$) (Figure 3). In patients with HR$^-$ tumors, the pCR rates for FEC-PH and FEC-DH were 65.4% and 45.5%, respectively ($P = .13$) (Figure 3). The clinical response rates by palpation were 79.6% in the FEC-PH arm and 76.6% in the FEC-DH arm, respectively (Table 2). Eighty-four patients received surgery. Seventy-two of these 84 patients received adjuvant trastuzumab. BCT was possible in 35 patients (71.4%) in the FEC-PH arm and 27 (57.4%) in the FEC-DH arm.

Safety

Grade 3/4 neutropenia was observed in 28.1% of 96 patients who received FEC, and 11 patients (11.5%) developed febrile neutropenia (Table 3). Adverse events that lead to hospitalization were reported in a total of 8 patients during FEC; 3 of these discontinued FEC. During the taxane phase, peripheral neurotoxicity was more common with PH than DH, whereas grade 3/4 neutropenia, febrile neutropenia, peripheral edema, and grade 1/2 mucositis and/or stomatitis were more common with DH than with PH. One patient developed grade 3 peripheral edema after 2 cycles of DH and stopped chemotherapy.

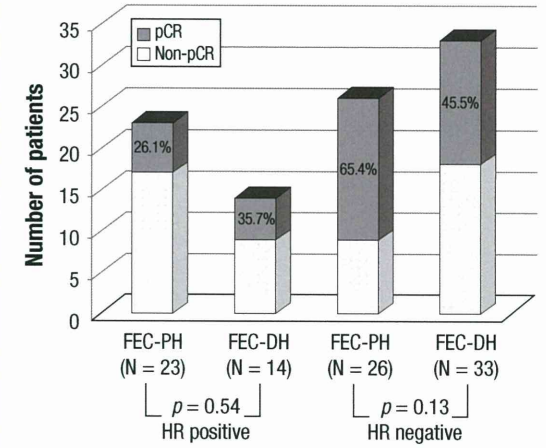
Cardiac events were observed in 4 patients. Two patients who received PH and 1 patient who received DH experienced grade 1 supraventricular arrhythmia. One patient developed grade 3 left ventricular systolic dysfunction with shortness of breath on exertion immediately after completion of 4 cycles of PH, accompanied by a decrease in LVEF to 39%. She had no history of cardiovascular disease but had received diuretic and beta-blocker

Table 1 Patient Characteristics

	FEC-PH (n = 49)	FEC-DH (n = 47)
Median Age (Range), y	51 (34-65)	53 (28-63)
Clinical Stage, No. (%) Patients		
IIA[a]	21 (42.9)	16 (34.0)
IIB	19 (38.8)	22 (46.8)
IIIA	9 (18.4)	9 (19.1)
Tumor, No. (%) Patients		
T1	1 (2.0)	1 (2.1)
T2	38 (77.6)	34 (72.3)
T3	10 (20.4)	12 (25.6)
Axillary Lymph Node-Positive Determination, No. (%) Patients		
Ultrasonography	27 (55.1)	33 (70.2)
SLNB	5 (10.2)	2 (4.3)
HER2 Status, No. (%) Patients		
IHC 3+	43 (87.8)	43 (91.5)
IHC 2+/FISH +	6 (12.2)	4 (8.5)
Hormone Receptor Status No. (%) Patients		
ER+/PgR+	12 (24.5)	4 (8.5)
ER+/PgR−	1 (20.4)	10 (21.3)
ER−/PgR+	1 (2.0)	0 (0)
ER−/PgR−	26 (53.1)	33 (70.2)

Abbreviations: DH = docetaxel; ER = estrogen receptor; FEC = 5-fluorouracil/epirubicin/cyclophosphamide; FISH = fluorescence in situ hybridization; HER2 = human epidermal growth factor receptor 2; IHC = immunohistochemistry; PgR = progesterone receptor; PH = paclitaxel; SLNB =sentinel lymph node biopsy.
[a] Including patients with tumor 2 cm in greatest dimension (T1c) and N0.

Figure 3 Pathologic Results According to Hormone Receptor (HR) Status. The Left Side Shows Pathologic Complete Response (pCR) in Patients With HR+ Disease and the Right Side Shows pCR in Those With HR− Disease



therapy for left ventricular systolic dysfunction. After 2 months, her symptoms had resolved with treatment, and she underwent BCT. Her LVEF had recovered to 58% one year after completion of PST. Four patients with adverse events were hospitalized during the trastuzumab plus taxane phase (1 patient received PH and 3 received DH). All remaining 84 patients who completed PST underwent surgery.

Twenty-nine (31.9%) of 91 patients who received trastuzumab plus taxane experienced infusion reactions during the first cycle of trastuzumab (14 patients with PH and 15 with DH). Among patients with infusion reactions, rigors and/or chills, fever, and pain were commonly observed; all events were grade 1 or 2. Eight (27.6%; 8.8% of all patients receiving trastuzumab plus taxane) of 29 patients who experienced infusion reactions during the first cycle of trastuzumab experienced a further infusion reaction during a later cycle.

Discussion

This study showed high pCR rates (46.9% with FEC-PH and 42.6% with FEC-DH) and that 62 (73.8%) of 84 patients undergoing surgery were able to receive BCT. The results of this study are consistent with the high pCR rates reported in previous trials that evaluated the combination of chemotherapy and trastuzumab as PST.[13–20,27] However, there was no significant difference in pCR rates between the 2 treatment groups. There was a trend to a higher rate of BCT with FEC-PH compared with FEC-DH, but the difference was not statistically significant. The small sample size may explain the lack of significant difference between the regimens.

The pCR rates were significantly higher in HR− tumors than in HR+ tumors with both treatments. This result is consistent with findings from several other studies of trastuzumab combined with anthracycline- and nonanthracyline-based regimens, including NOAH (concurrent anthracycline/taxane)[14] NeoSphere (docetaxel),[28] and NeoALTTO (paclitaxel).[29] Analysis of the data from these studies suggests that patients with HER2+ and HR− disease will obtain greatest benefit from a trastuzumab-containing chemotherapeutic regimen. Although other findings, reported by Peintinger et al[30] and Buzdar et al[13] contrast with results from NOAH, NeoSphere, NeoALTTO and the present study, the larger studies have demonstrated higher pCR rates in HR− than HR+ breast cancer after trastuzumab-based regimens. Moreover, after the initial conclusions from Buzdar[13] and Peintinger,[30] additional data from the M.D. Anderson group demonstrated a statistically higher pCR rate in HR− than HR+ breast cancer (61.1% vs. 38.9%, respectively). Recently, von Minckwitz et al[31] presented data from a meta-analysis of 7 trials (n = 6377) of neoadjuvant therapy, including anthracyclines and taxanes with or without trastuzumab, that showed that pCR is a surrogate for survival in patients with HER2+ HR− breast cancer but not in those with HR+ disease. It is also relevant to note that, in large trials of adjuvant therapy, prognosis is not different between HR− and HR− tumors.[8–10] Therefore, longer follow-up is required in the setting of PST before definitive conclusions can be made about the importance of HR status and therapeutic outcomes. Further clinical and translational

Table 2 Clinical and Pathologic Response Rates

	FEC-PH (n = 49)		FEC-DH (n = 47)	
	No. Patients	%	No. Patients	%
Completion of PST	43	87.8	41	87.2
Clinical Response by Palpation[a]	39	79.6	36	76.6
CR	30	–	28	–
PR	9	–	8	–
SD	0	–	2	–
PD	1	–	1	–
Breast Surgery	43	87.8	41	87.2
Mastectomy	8	–	14	–
BCT	35	71.4	27	57.4
AxLND	36	–	36	–
Lymph Nodes (Pathologic)				
Negative	32	–	28	–
Positive	4	–	8	–
SLNB Without AxLND[b]	6	–	4	–
Pathologic CR[c] ITT	23	46.9	20	42.6
Per protocol	23/43	53.5	20/40	50.0
DCIS in Breast	10	–	14	–

Abbreviations: AxLND = axillary lymph node dissection; BCT = breast conserving therapy; CR = complete response; DCIS = ductal carcinoma in situ; DH = docetaxel; FEC = 5-fluorouracil/epirubicin/cyclophosphamide; PD = progressive disease; PH = paclitaxel; PR = partial response; PST = preoperative systemic therapy; SD = stable disease; SLNB = sentinel lymph node biopsy.

[a] Including 7 patients not evaluable for response (4 in the FEC-PH group and 3 in the FEC-DH group).

[b] SLNB was performed before PST.

[c] Including one patient not evaluable for pathologic response in the FEC-DH group.

research on the interaction between HR status, HER2 status, and pCR is warranted.

In the NOAH trial, the addition of trastuzumab to preoperative chemotherapy and postoperative trastuzumab for 52 weeks improved disease-free survival relative to chemotherapy alone (71% vs. 56% at 3 years; $P = .006$).[14] It remains to be determined whether the addition of postoperative trastuzumab will further improve disease-free and overall survival in patients who have achieved a pCR with sequential anthracycline and taxane plus trastuzumab. However, longer survival has been demonstrated in patients achieving pCR compared with those not achieving pCR, even in the $HER2^+$ subgroup,[21,22] although it may be different in patients with HR^- and HR^+ breast cancer, and needs to be viewed cautiously.

In studies with trastuzumab and nonanthracycline-containing regimens (eg, combination of taxane and platinum), pCR rates have ranged from 17% to 76%.[16–20] Studies of preoperative concurrent anthracycline and taxane with trastuzumab (for 12-24 weeks) have shown pCR rates of 38%-66%.[13–15] Results of these studies suggest that concurrent anthracycline and trastuzumab has a considerable antitumor effect, although, cardiotoxicity remains a concern with this regimen. A review of the medical literature provides reassurance that the cardiac toxicity of concurrent trastuzumab and anthracycline is acceptable and manageable.[13–15] The dose of anthracycline is an important factor in cardiac safety. In the current study, the dose of anthracycline (epirubicin 100 mg/m^2 for 4 cycles was higher than in previous studies that used doxorubicin (60 mg/m^2 for 3 cycles) or epirubicin (75 mg/m^2 for 4 cycles). Therefore, cardiotoxicity may be avoided by reducing the dose of anthracycline when used in combination with trastuzumab. Sequential administration of trastuzumab after anthracycline, as used in the present study, is also an appropriate approach to reduce the risk of cardiotoxicity. However, it might relate to an administration order of anthracycline and taxane, not concurrent administration of anthracycline and trastuzumab, because concurrent administration of anthracycline and trastuzumab has less cardiotoxicity in the report by Buzder et al.[13] Longer follow-up is required to further evaluate the cardiac safety profile of anthracyline-trastuzumab PST to determine a preferable method; dose reduction or sequential administration, including an administration order of anthracycline and taxane.

Twelve (12.5%) of 96 patients in our study did not complete PST. The major reasons for discontinuation of PST were chemotherapy-related adverse events. One patient in the FEC-PH group experienced grade 3 left ventricular systolic dysfunction. A limitation of this study was the evaluation of LVEF by echocardiogram only at study entry and completion of surgery if patients showed no symptoms of left ventricular failure. Experience of cardiotoxicity in this study suggests that LVEF by echocardiogram should be monitored at completion of FEC and again at completion of trastuzumab plus taxane therapy. Long-term follow-up of cardiotoxicity is required for patients in this study who received preoperative and adjuvant trastuzumab.

Because FEC-PH and FEC-DH demonstrated similar efficacy overall, differences in safety profile are important in determining the most appropriate PST regimen to offer to candidates for BCT. Paclitaxel was associated with an increased incidence of peripheral neuropathy, whereas use of docetaxel produced greater neutropenia, febrile neutropenia, peripheral edema, and mucositis. The choice of PST, therefore, should be individualized according to patient characteristics and preferences. Although analysis of data suggested a possible advantage for paclitaxel in terms of higher pCR in the subgroup of patients with HR^- disease and a higher rate of BCS, the differences were not statistically significant.

Conclusion

FEC, followed by concurrent trastuzumab with taxane (weekly paclitaxel or 3-weekly docetaxel), seems active and feasible as PST for $HER2^+$ breast cancer. There was no significant difference in pCR rate between FEC-PH and FEC-DH, although there was a trend to a higher rate of pCR with the paclitaxel-containing regimen in patients with HR^- breast cancer. Whether this trend is clinically significant is not yet known. Long-term follow-up of patients in this study treated with preoperative and adjuvant trastuzumab will provide further information on cardiac safety and disease-free survival.

Randomized comparisons of PST regimens, comprising various permutations of anthracyclines, taxanes, and platinum administered with concurrent and/or sequential trastuzumab, together with long-term follow-up of cardiac safety and disease-free

Table 3 Adverse Events During Primary Systemic Therapy (NCI CTCAE version 3.0 grading)

Toxicity	FEC-PH (grade, %)				FEC-DH (grade, %)			
	FEC (n = 49)		PH (n = 46)		FEC (n = 47)		DH (n = 45)	
	All	3/4	All	3/4	All	3/4	All	3/4
Hematologic								
Neutropenia	46.9	28.6	39.1	2.2	36.2	27.7	15.6	8.9
Febrile neutropenia	12.2	12.2	0	0	10.6	10.6	6.7	6.7
Anemia	44.9	2.0	54.3	0	44.7	0	55.6	2.2
Thrombocytopenia	4.1	0	0	0	8.5	0	2.2	0
Nonhematologic								
Anorexia	46.9	2.0	8.7	0	40.4	0	17.8	0
Nausea/vomiting	87.8	2.0	21.7	0	91.5	0	24.4	0
Vomiting	44.9	4.1	15.2	0	65.9	6.4	15.6	0
Diarrhea	12.2	0	30.4	0	19.1	0	35.6	0
Mucositis and/or stomatitis	53.1	0	19.6	0	61.7	0	57.8	0
Taste alteration	38.8	–	41.3	–	44.7	–	53.3	–
Fatigue	49.0	0	50.0	0	68.1	2.1	64.4	0
Peripheral neurotoxicity	4.1	0	95.7	4.3	8.5	0	51.1	0
Arthralgia and/or myalgia	0	0	39.1	0	0	0	42.2	0
Peripheral edema	6.1	0	39.1	0	12.8	0	62.2	2.2
Infection	6.1	0	6.5	0	8.5	0	13.3	0
Elevated AST, ALT	38.8	2.0	47.8	0	25.5	0	31.1	0
Arrhythmia	0	0	4.3	0	2.1	0	2.2	0
Left ventricular dysfunction	0	0	2.2	2.2	0	0	0	0
Hyperglycemia	0	0	0	0	0	0	2.2	2.2
Nail changes	63.3	–	73.9	–	51.1	–	60.0	–
Skin rash	16.3	0	21.7	0	4.3	0	26.7	0
Infusion reaction	–	–	30.4	0	–	–	33.3	0

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; FEC = 5-fluorouracil/epirubicin/cyclophosphamide; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; PD = progressive disease; PH = paclitaxel.

survival are required before definitive recommendations can be made for patients with $HER2^+$ breast cancer.

Clinical Practice Points

- PST is a standard management option for patients with operable breast cancer and can facilitate breast conservation.
- The addition of trastuzumab to primary systemic chemotherapy achieves a high rate of pCR in patients with $HER2^+$ breast cancer, but the optimal treatment regimen has not yet been defined.
- Concurrent use of trastuzumab and anthracycline-based therapy must be used with caution because of the potential risk for cardiac toxicity.
- Preoperative treatment regimens comprising FEC followed by either trastuzumab and paclitaxel or trastuzumab and docetaxel were similarly effective in patients with $HER2^+$ breast cancer and both achieved high rates of pCR.
- The pCR rates were higher in patients with HR^- tumors than in those with HR^+ disease.
- The paclitaxel-containing regimen showed a trend to a higher pCR rate in patients with HR^- tumors and a higher rate of breast conserving surgery compared with the docetaxel-containing regimen.
- Sequential use of trastuzumab-taxane after FEC was generally well tolerated, although cardiac safety remains an important consideration. It is important that LVEF is monitored at study entry, at the completion of FEC, and again at the completion of trastuzumab-taxane combination therapy.

Acknowledgments

This study was presented in part at the 45th annual meeting of the American Society of Clinical Oncology, Orlando, Florida, June 1, 2009. Trastuzumab was provided as an investigational drug by Chugai Pharmaceutical Co, Ltd, Tokyo, Japan. This study was supported by Health and Labour Sciences Research Grants (Clinical Cancer Research) of the Ministry of Health, Labor, and Welfare (MHLW). The study was performed as a

registration-directed trial in accordance with the Good Clinical Practice guideline (Enforcement Regulation No. 106 of the MHLW (revised GCP) dated May 15, 2003), which is laid down by the revised Pharmaceutical Affairs Act in Japan (No. 96 of the MHLW dated on 31 July 31, 2002).

Disclosure

The authors have stated that they have no conflicts of interest.

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