analysis. The article contains no information about the interrelatedness of PF, EF, and FA.

Kart and Ford (2002) used the same patients of Ford et al. (2001). They ran separate principal component analyses in the two samples. They obtained seven principal components (factors) for the 30 items of the QLQ-C30. In the Caucasian sample, one factor replicated EF and a second factor consisted of FA and four items of PF. In the African American group, EF and CF were replicated as separate factors. In both groups, the remaining factors show mixtures of the items of various scales and symptoms.

Gotay et al. (2002) conducted three studies on the content validity of the QLQ-C30. Study 2 used confirmatory factor analysis on the data of 367 heterogeneous cancer patients in Hawaii. One latent factor was found that could explain the relations between the five functioning scales, QL, and a variable that counted the number of symptoms endorsed by a patient. By combining PF and RF into one scale, the model was improved and showed excellent fit.

In a study of 150 women with metastatic breast cancer McLachlan et al. (1999) analyzed the intercorrelations among the 12 items of EF, CF, RF, SF, and QL. They found two principal components that were labeled "emotional distress" {EF, CF} and "functional ability" {RF, SF, QL}.

Using the data before and after chemotherapy of 535 patients with several types of cancer, Osaba et al. (1994) performed several factor analyses on the items of the nine multi-item scales of the QLQ-C30. They reported nine orthogonal factors that reproduced the nine postulated scales reasonably well. For the total group of patients, the matrix of intercorrelations among the 15 QLQ-C30 scales showed high correlations ($|r| > .60$) between PF, RF, and FA and between FA and QL.

Studies of the Interrelations among the QLQ-C30 Scale

Boehmer and Luszczynska (2006) tested the model of Fayers, Hand, Bjordal, and Groenvold (1997) who proposed that the functioning scales of the QLQ-C30 are indicators of the patient's quality of life, whereas the symptom scores are seen as causal variables that influence quality of life. Boehmer and Luszczynska tested two structural equation models. The first model hypothesized that there is one latent factor "symptomatology" underlying nine latent variables for the symptom scales, which are supposed to influence one latent construct HRQOL. This construct in its turn effects separate latent factors for PF, RF, CF, SF, and EF, which are measured by the corresponding items. The second model hypothesized that both the functioning and the symptom scales can be explained by one underlying latent construct. The first model was supported by confirmatory factor analyses, although it was not significantly better than the simpler model in which one latent factor underlies all scales and items of the QLQ-C30.

Study 3 of Gotay et al. (2002) used the same 367 heterogeneous cancer patients as Study 2. Factor analysis of QL, CF, EF, SF, two combinations of PF and RF items, and 22 new questions, yielded one single factor with eigenvalue >1, which demonstrates the connectedness of the six QLQ-C30 scales.

Gundy et al. (2012) used the data of 4541 cancer patients who were heterogeneous with respect to cancer type and nationality to compare seven structural equation models that differed with regard to the postulated relations between 14 QLQ-C30 scales (FI was excluded) and the number and structure of explanatory factors. The best fitting model, labeled the Physical/Mental health model, contained three correlated higher-order factors: Physical Health, Mental Health, and QL. PF, NV, DY, AP, CO, and DI were explained by Physical Health; CF and EF were explained by Mental Health. To explain RF, SF, FA, PA, and SL both factors were needed. The estimated correlation between Physical Health and Mental Health was .74; the correlations of those factors with QL were not reported.

In a sample of 177 heterogeneous Norwegian cancer patients, Ringdal and Ringdal (1993) used Mokken Scale Analysis on subsets of the 30 items. They replicated the CF, EF, SF, QL, PA, and FA scales and found evidence that PF and RF belonged to one "personal functioning scale" and that NV and AP could be combined. Principal component analysis of the above scales except QL, yielded two oblique factors ($r = .47$) with high loadings of {PF & RF}, {NV & AP}, PA, and FA on the first factor, and high loadings of FA, CF, EF, and SF on the second factor. QL was related to both factors. The authors interpreted the first factor as a physical one and the second factor as psychological. They regarded the positive correlation of these factors "as a weak argument for the existence of a general QOL dimension" (Ringdal & Ringdal, 1993, p. 139).

Using data from 187 women with advanced breast cancer, van Steen et al. (2002) found three principal components in 12 scales of the QLQ-C30 (CO, DI, and FI were not studied). The first factor contained high absolute loadings of PF, RF, SF, QL, and PA. The second factor showed a cluster of AP, DY, FA, NV and CF. The third factor primarily consisted of SL. EF had substantial loadings on Factor 2 and Factor 3.

Studies Relating QLQ-C30 Scales and Items with Other Instruments

In a study of 201 head and neck cancer patients, Arraras et al. (2002) reported correlations of .67 and .70 between PF and RF on two subsequent occasions. The correlations between PF and FA were −.49 and −.67, between RF and SF .49 and .70, and between RF and FA −.40 and −.68.

A study of 137 prostate cancer patients by Arraras Urdaniz et al. (2008) yielded correlations between PF and RF of .65 on two subsequent occasions.

The correlations between PF and SF were .57 and .50. PF and FA correlated −.71 and −.63, RF and FA −.65 and −.62, and EF and FA −.51 and −.57.

Henoch et al. (2009) analyzed the correlations among those items of the QLQ-C30 that were also present in the Symptom Distress Scale (McCorkle & Young, 1978). They obtained three clusters of items. The first cluster—"mood"—contained two items of the EF scale, one item of the CF scale, and SL. The second cluster—"pain"—contained FA, AP, one of the PA items, one of the NV items, and the mean score of the DI and CO items. The third cluster—"respiratory"—consisted of DY and the non-QLQ-C30 item "cough".

King et al. (1996) performed a multitrait-multimethod study on the scales of the QLQ-C30 and seven subscores of the Function Living Index-Cancer (FLIC; Schipper, Clinch, McMurray, & Levitt, 1984). The correlations among the QLQ-C30 scales were substantial and suggested the existence of three clusters {RF, PF}, {EF, SF}, and {QL, FA, PA}, which possibly could be merged into one cluster.

Using a structural equation model for the effects of socioeconomic factors on the HRQOL of 130 Japanese cancer survivors, Kobayashi et al. (2008) presented evidence for one latent HRQOL factor underlying PF, RF, EF, CF, and SF.

Pagano and Gotay (2006) applied item response theory to the data of 366 heterogeneous cancer patients in Hawaii to obtain a unidimensional scale from the items of the QLQ-C30 and 35 items of two other instruments. The resulting 22-item scale contained 15 items from the QLQ-C30: the two QL items, one PF items, one RF items, both SF items, all four EF items, all three FA items, one PA items, and the item for AP.

Strasser et al. (2009) used PF, EF, and CF scores of 61 patients with advanced cancer in a principal component analysis with several scales of other measuring instruments, and obtained two factors—"cognitive" and "physical"—with high loadings of CF and PF, respectively. EF had a high loading (.71) on the first factor and a substantial loading (.49) on the second factor.

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CLINICAL TRIAL

Randomized phase II study of weekly paclitaxel with and without carboplatin followed by cyclophosphamide/epirubicin/5-fluorouracil as neoadjuvant chemotherapy for stage II/IIIA breast cancer without HER2 overexpression

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Abstract Addition of carboplatin to neoadjuvant chemotherapy in HER2-negative breast cancer may improve pathological complete response (pCR) rates. We evaluated the efficacy and safety of carboplatin and weekly paclitaxel (wPTX) followed by cyclophosphamide, epirubicin, and 5-fluorouracil (CEF) as neoadjuvant chemotherapy for HER2-negative breast cancer. Patients with stage II/IIIA HER2-negative breast cancer were randomly assigned to preoperatively receive CP-CEF (four 3-week cycles of carboplatin [area under the curve 5 mg/mL/min, day 1] and wPTX [80 mg/m^2, day 1, 8, 15] followed by four 3-week cycles of CEF [500/100/500 mg/m^2] or P-CEF (four cycles of wPTX followed by four cycles of CEF). The primary objective was pCR rate. Of 181 eligible patients, 89 were randomly assigned to the CP-CEF and 92 to the P-CEF. Two patients in each arm refused to receive neoadjuvant chemotherapy. Overall 88 patients in the CP-CEF and 91 patients in the P-CEF were assessable for efficacy and safety. The pCR rate in the CP-CEF was significantly higher than that in the P-CEF (31.8 vs. 17.6 %, one-sided $P = 0.01$). Among patients with triple-negative breast cancer, the pCR rate in the CP-CEF was significantly

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higher than that in the P-CEF [61.2 (23/37) vs. 26.3 % (10/38), $P = 0.003$]. Grade 3–4 neutropenia was observed in the CP-CEF more frequently than in the P-CEF (65.9 vs. 38.5 %). Adding carboplatin to neoadjuvant wPTX followed by CEF for HER2-negative breast cancer improved the pCR rate and exacerbated hematotoxicity.

Keywords Breast cancer · Carboplatin · HER2 negative · Neoadjuvant chemotherapy

Introduction

Neoadjuvant chemotherapy is a widely accepted treatment option for patients with operable breast cancer [1, 2]. Currently, anthracyclines and taxanes in sequence or in combination are recommended for patients with HER2-negative disease, and anthracyclines followed by combinations of taxanes and trastuzumab are recommended for patients with HER2-positive disease [3–5]. Pathological complete response (pCR), which is defined as disappearance of all invasive carcinomas in primary and axillary nodes and is associated with long-term survival, occurs in about 15–20 % of patients with HER2-negative disease treated with anthracyclines and taxanes [3, 4].

Several new chemotherapeutic regimens have been evaluated in patients with HER2-negative disease. Adding capecitabine or gemcitabine to epirubicin and cyclophosphamide followed by taxane therapy did not improve pCR rates in the neoadjuvant setting [6, 7]. Carboplatin, a platinum compound, has yielded response rates of 20–35 % in phase II studies of previously untreated patients with metastatic breast cancer (MBC) [8–10]. In patients with HER2-positive disease, combinations of carboplatin, taxanes, and trastuzumab are active in both the adjuvant and metastatic settings [11, 12]. In a phase III study of MBC patients who previously received anthracycline-based adjuvant chemotherapy, ~70 % of whom had HER2-negative disease, first-line therapy consisting of triweekly carboplatin and paclitaxel resulted in similar progression-free survival as gemcitabine plus docetaxel [13]. Weekly paclitaxel (wPTX) followed by cyclophosphamide, epirubicin, and 5-fluorouracil (CEF) is a commonly used neoadjuvant chemotherapy regimen for patients with HER2-negative breast cancer [14]. Recently, triple-negative breast cancers (TNBC) were classified into six subtypes depending on gene profiles, and basal-like 1–2 subtypes were suggested as highly sensitive to cisplatin in the vitro study [15]. The previous randomized phase II study suggested a potential benefit of platinum for metastatic TNBC [16].

We hypothesized that carboplatin would enhance the anti-tumor activity of wPTX and that this combination would improve pCR rates over the conventional regimens of wPTX followed by CEF. We conducted this randomized phase II trial to assess the efficacy and safety of adding carboplatin to wPTX followed by CEF in the neoadjuvant setting for patients with HER2-negative breast cancer.

Patients and methods

Patient eligibility

Eligible patients had previously untreated, unilateral, histologically confirmed, invasive, non-inflammatory, breast carcinoma. Histologic confirmation of invasive cancer was performed by core needle biopsy (CNB). HER2-negative disease was defined as a score of 0 or 1 + by immunohistochemistry (IHC) or HER2 gene copy: chromosome 17 ratio of <2.0 by fluorescence in situ hybridization (FISH). Patients with a tumor >2.0 cm at the largest dimension by ultrasonography, or ≤2.0 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 to be clinically node positive. Patients with T4, N3, (supraclavicular lymph node), or distant metastatic disease (M1) were excluded from this study.

Other requirements included age 18–70 years, ECOG performance status 0–2, adequate bone marrow function (absolute granulocyte count ≥1,500/mm^3 and platelet count ≥100,000/mm^3), liver function (total bilirubin ≤1.5 mg/dL and liver transaminase [aspartate aminotransferase (AST) and alanine aminotransferase (ALT)] ≤60 IU/L), and renal function (serum creatinine ≤1.5 mg/dL), and written informed consent. Patients with a history of ischemic cardiac disease were excluded. Patients with clinically negative axillary lymph nodes had the option of undergoing pretreatment sentinel lymph node biopsy (SLNB).

Study design and neoadjuvant chemotherapy

This was a randomized, multicenter (10 institutions), non-blinded phase II study. The study design is shown in Fig. 1. Enrolled patients were randomly assigned to receive either wPTX (P) followed by CEF (P-CEF arm) or combination carboplatin and wPTX (CP) followed by CEF (CP-CEF arm) by the minimization method, with balancing of the treatment arms according to disease status (stage II vs. IIIA), hormone receptor (HR) status, and institution. Paclitaxel was administered at 80 mg/m^2 IV over 1 h on days 1, 8, and 15 every 3 weeks for four cycles. Carboplatin and wPTX were administered at area under blood concentration

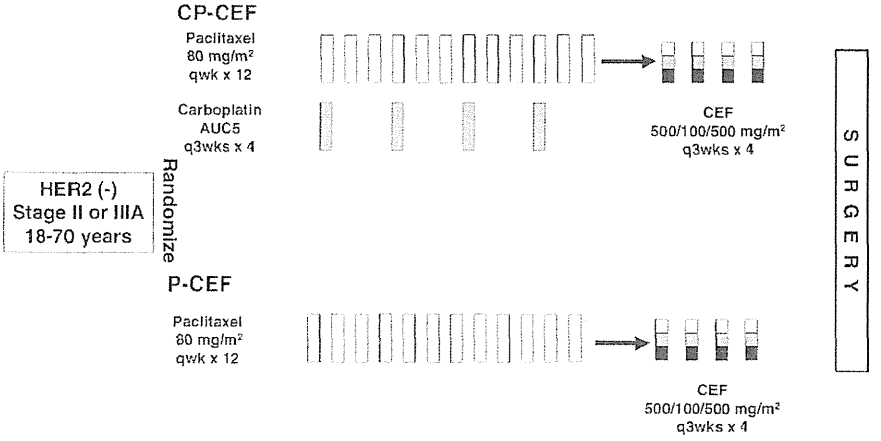

Fig. 1 Study design. *CPA* cyclophosphamide, *EPI* epirubicin, *5-FU* 5-fluorouracil, and *HER2* human epidermal growth factor receptor-2

time curve (AUC) 5 mg/mL/min IV over 1 h on day 1 and at 80 mg/m^2 IV over 1 h on days 1, 8, and 15, respectively, every 3 weeks for four cycles. CEF consisted of CEF (500/100/500 mg/m^2) IV on day 1 every 3 weeks for four cycles. Carboplatin was provided by Bristol-Myers Squibb K.K., Tokyo, Japan as an investigational drug.

If a patient developed grade $\geq$3 febrile neutropenia, thrombocytopenia <25,000/mm^3, or grade $\geq$3 non-hematologic toxicity while receiving CP or CEF, the doses of carboplatin and epirubicin were reduced by 20 and 25 %, respectively, in subsequent cycles. The doses of paclitaxel during CP and P were reduced by 25 % in subsequent cycles if a patient developed grade 3 neurotoxicity. Before administration of the following cycle of CP, P, or CEF, patients were required to have a granulocyte count $\geq$1,500/mm^3, platelet count $\geq$75,000/mm^3, and no non-hematologic toxicity of grade $\leq$2 (excluding alopecia). Before administration of CP on day 8 and 15, patients were required to have a granulocyte count $\geq$500/mm^3, platelet count $\geq$75,000/mm^3, and peripheral neuropathy of grade $\leq$2. If toxicity did not improve within 2 weeks on the P or CP regimen, chemotherapy was discontinued and initiation of CEF was recommended. If toxicity did not improve within 2 weeks on CEF, chemotherapy was discontinued and surgery was recommended.

Therapy after neoadjuvant chemotherapy

Patients who were considered candidates for breast-conserving therapy (BCT) were offered lumpectomy. Axillary lymph node dissection (AxLND) was mandatory, except in patients diagnosed as having no metastases by SLNB before neoadjuvant chemotherapy. Surgery was performed within 8 weeks after completion of preoperative chemotherapy. All patients who underwent BCT received whole-breast irradiation. After completion of neoadjuvant chemotherapy and surgery, patients with HR-positive disease received adjuvant endocrine therapy.

Study evaluation and criteria

The HER2 status of CNB specimens was determined by IHC and/or FISH performed at each institution before study enrollment, and was not subject to central review. HR status [estrogen receptor (ER) and progesterone receptor (PgR)] of CNB specimens was assessed by IHC, for which $\geq$10 % staining of cancer cell nuclei was diagnosed as positive. HR positivity was defined as ER-positive and/or PgR-positive disease. Histological grade was scored according to the modified Scarff–Bloom–Richardson classification [17]. After completion of neoadjuvant chemotherapy, resected specimens and CNB specimens were evaluated centrally by 3 breast pathologists. A pCR was defined as the absence of viable invasive tumor in both the breast and axillary nodes. Patients with residual ductal carcinoma in situ (DCIS) in the breast and no viable invasive tumor in the axillary nodes were also classified as having a pCR. Clinical response was evaluated by palpation and caliper after each cycle according to the Response Evaluation Criteria In Solid Tumors version 1.1. All adverse events were evaluated according to the Common Terminology Criteria for Adverse Events version 4.03.

Endpoints and statistical analysis

The primary endpoint was the pCR rate. Secondary endpoints included disease-free survival, clinical response rate, breast conservation rate, and safety. Efficacy and safety analysis were performed in the intent-to-treat (ITT) population, which consisted of subjects fulfilling the study inclusion criteria who had received at least one dose of study chemotherapy. The per-protocol population consisted of subjects who had completed chemotherapy and underwent surgery in this study without serious violations of the inclusion criteria.

Based on previous studies of neoadjuvant anthracyclines and taxanes, patients with HER2-positive disease account

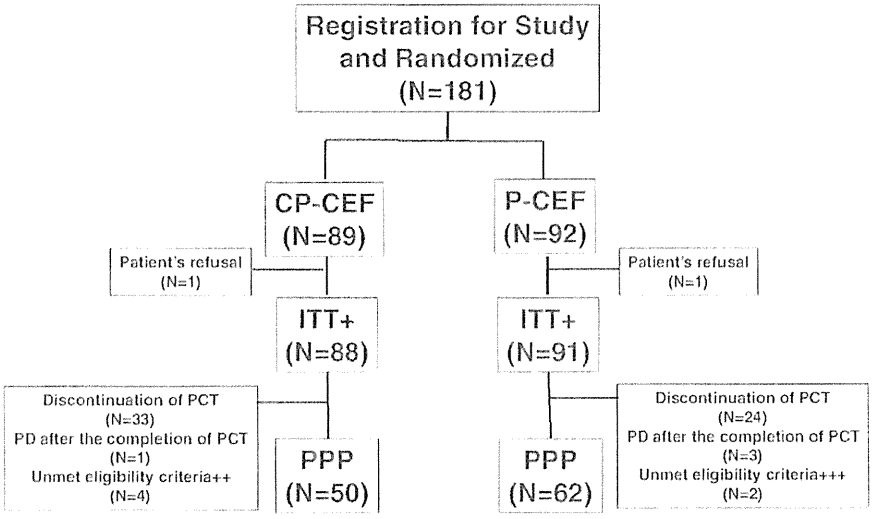

Fig. 2 CONSORT flow diagram. Disposition of study participants. + 6 of the 61 patients who discontinued neoadjuvant chemotherapy or showed disease progression after the completion of chemotherapy were diagnosed as ineligible by pathological central review (3 patients in the CP-CEF and 3 patients in the P-CEF arm), ++ patients who were diagnosed as ineligible by pathological central review, and +++ patients who were determined to have Stage IIIC disease after enrollment. *ITT* intent to treat, *PCT* preoperative chemotherapy by study protocol, and *PPP* per-protocol population

for 6–30 % of the treatment population, and pCR rates (defined in the same manner as the present study) ranged from 16 to 26 % [4, 6, 13]. The present study was designed for patients with HER2-negative disease, and P-CEF was expected to produce a pCR rate of 15 %. The study was originally planned to enroll 110 patients in each treatment arm in order to detect a 30 % increase in pCR in the CP-CEF arm with 90 % power using the Pearson's chi squared test and one-sided 10 % significance level. Due to an administrative reason (the termination of financial support due to the end of a government-sponsored clinical trial program), the revised sample size with 87 % power was a total of 180 patients. Study accrual was not stopped on the basis of an interim analysis. An exploratory logistic regression analysis was conducted to examine the influence of clinical stage (II, IIIA), clinical nodal status (positive, negative), histological grade (grade 1, 2, 3), HR status (positive, negative), and age (<50, ≥50 years) on pCR. The primary test of the pCR rate was reported as one-sided and other reported *P* values were two-sided tests. Analyses were conducted using JMP® software version 8.0.2 (SAS Institute Inc., Cary, NC, USA).

Results

Patient characteristics

Between March 2010 and September 2011, 181 patients entered into this study. Of these, 88 patients treated with CP-CEF and 91 treated with P-CEF were evaluable in the ITT population. Two patients in each arm refused to receive neoadjuvant chemotherapy. Furthermore 38 patients in the CP-CEF arm and 29 patients in the P-CEF arm were excluded from the per-protocol population (Fig. 2). According to central review, 9 patients were considered ineligible [HER2 score 2 + by IHC and FISH not done ($n = 6$), CNB specimen not evaluable for invasive component ($n = 1$), and CNB specimen not evaluable ($n = 2$)]. Two patients had proven stage IIIC disease after enrollment.

Characteristics of the ITT population are shown in Table 1. The median age was 47 years old. Distributions of tumor size, nuclear grade, and clinical axillary node status were similar; and more than 95 % of patients were diagnosed with invasive ductal carcinoma in the two arms. In the both arms, 42 % of patients had HR-negative (and thus triple-negative) tumors and 41 % had ER- and PgR-positive disease.

Treatment exposure

In the CP-CEF and P-CEF arms, 55 of 88 patients (62.5 %) and 67 of 91 patients (73.6 %), respectively, received all of the planned treatment cycles. In the CP-CEF arm, 64 patients (72.7 %) completed four cycles of CP; while in the P-CEF arm, 82 patients (90.1 %) completed four cycles of P (Table 2). In the CP-CEF arm, 33 patients did not complete chemotherapy due to adverse events ($n = 29$) or disease progression ($n = 4$). In the P-CEF arm, 24 patients

Table 1 Characteristics of eligible patients treated with neoadjuvant chemotherapy ($n = 179$)

	CP-CEF ($n = 88$)	P-CEF ($n = 91$)
Age (range; years)	47 (30–69)	47 (30–70)
<50	52 (59.1 %)	51 (66.0 %)
≥50	36 (40.9 %)	40 (44.0 %)
Menopausal status		
Premenopausal	60 (68.8 %)	54 (59.3 %)
Postmenopausal	28 (31.2 %)	37 (40.7 %)
Performance status 0	88 (100 %)	91 (100 %)
Clinical stage		
II	71 (80.7 %)	75 (82.4 %)
IIIA	17 (19.3 %)	14 (15.4 %)
IIIC	0 (0 %)	2 (2.2 %)[a]
Clinical tumor size (cm)		
≤2.0	2 (2.3 %)	4 (4.4 %)
2.1–5.0	64 (72.7 %)	63 (69.2 %)
≥5.1	22 (25.0 %)	24 (26.4 %)
Median, cm (range)	4.0 (1.0–11.0)	4.0 (1.5–8.0)
Clinical axillary nodal status		
Negative	32 (36.4 %)	30 (33.0 %)
Positive	56 (63.6 %)	61 (67.0 %)
Pathology		
Invasive ductal carcinoma	84 (95.5 %)	89 (97.8 %)
Invasive lobular carcinoma	3 (3.4 %)	0 (0 %)
Others	1 (1.1 %)	2 (2.2 %)
Histological grade		
1	16 (18.2 %)	13 (14.3 %)
2	29 (33.0 %)	35 (38.5 %)
3	43 (48.9 %)	43 (47.3 %)
Hormone receptor status		
ER−/PgR−	37 (42.0 %)	38 (41.8 %)
ER+/PgR+	36 (40.9 %)	37 (40.7 %)
ER+/PgR−	13 (14.8 %)	14 (15.4 %)
ER−/PgR+	2 (2.2 %)	2 (2.2 %)

CP-CEF carboplatin and weekly paclitaxel followed by cyclophosphamide/epirubicin/5-fluorouracil, *P-CEF* weekly paclitaxel followed by cyclophosphamide/epirubicin/5-fluorouracil, *ER* estrogen receptor, *PgR*, progesterone receptor

[a] These 2 patients were determined to have clinical stage IIIC disease after enrollment

did not complete chemotherapy due to adverse events ($n = 6$), refusal ($n = 6$), ineligibility ($n = 2$), or disease progression ($n = 10$).

Of 88 patients treated with CP, 65 (73.9 %) required delayed administration or at least one dose reduction of paclitaxel, 18 of whom required one dose reduction of carboplatin. Of 91 patients treated with P, 28 (30.8 %) required delayed administration or at least one dose reduction of paclitaxel. Sixteen patients in each treatment arm required at least one dose reduction of CEF.

Table 2 Treatment exposure, clinical response, breast surgery, and adjuvant therapy

	CP-CEF ($n = 88$)	P-CEF ($n = 91$)
Completion of each treatment cycle		
CP or P 1st cycle	87 (98.9 %)	89 (97.8 %)
CP or P 2nd cycle	81 (92.0 %)	88 (96.7 %)
CP or P 3rd cycle	73 (83.0 %)	85 (93.4 %)
CP or P 4th cycle	64 (72.7 %)	82 (90.1 %)
CEF 1st cycle	59 (67.0 %)	76 (83.5 %)
CEF 2nd cycle	58 (65.9 %)	75 (82.4 %)
CEF 3rd cycle	58 (65.9 %)	69 (75.8 %)
CEF 4th cycle	55 (62.5 %)	67 (73.6 %)
Clinical response rate		
CR	40 (45.5 %)	30 (33.0 %)
PR	34 (38.6 %)	34 (37.4 %)
SD	6 (6.8 %)	5 (5.5 %)
PD	5 (5.7 %)	13 (14.3 %)
NE	3 (3.4 %)	9 (9.9 %)
Breast surgery	88 (100 %)	89 (98.9 %)
Breast-conserving surgery	54 (61.4 %)	59 (64.8 %)
Axillary lymph nodes dissection	59 (67.0 %)	64 (70.3 %)
No. of nodes		
Negative	21	27
1–3 nodes	20	27
4–9 nodes	11	9
≥10 nodes	7	1
Adjuvant radiotherapy	50 (56.8 %)	56 (61.5 %)
Adjuvant endocrine therapy	37 (42.0 %)	33 (36.3 %)

CP carboplatin and weekly paclitaxel, *CEF* cyclophosphamide/epirubicin/5-fluorouracil, *P* weekly paclitaxel, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease

Efficacy

After chemotherapy, 88 patients in the CP-CEF arm and 89 patients in the P-CEF arm underwent breast surgery. Two patients in the P-CEF arm did not undergo surgery due to proven stage IIIC disease after enrollment ($n = 1$), and patient refusal to continue treatment due to adverse events experienced during CEF ($n = 1$). The breast conservation rates were 61.4 % in the CP-CEF arm and 64.8 % in the P-CEF arm. Fifty-nine patients (67.0 %) in the CP-CEF arm and fifty-nine patients (67.0 %) in the P-CEF arm underwent AxLND (Table 2).

The overall clinical response rate to CP-CEF was significantly higher than that to P-CEF (84.1 vs. 70.3 %, $P = 0.03$). Disease progression was observed in 4 patients who received CP-CEF (3 during CP and 1 during CEF) and 10 patients who received P-CEF (8 during P and 2 during CEF). After completion of neoadjuvant chemotherapy, 1

Table 3 Odds ratios for pCR rates according to subgroups

Subgroup	Non-pCR[a] No.	pCR No. (%)	Univariative analysis Odds ratio (95 % CI)	*P* value
Arm				
CP-CEF	60	28 (31.8)	2.19 (1.08–4.41)	0.04
P-CEF	75	16 (17.6)	1.00	
Age (years)				
<50	75	28 (27.2)	0.71 (0.35–1.44)	0.38
≥50	60	16 (21.1)	1.00	
Clinical T stage				
T1–2	95	39 (29.1)	1.00	0.02
T3	40	5 (11.1)	0.30 (0.11–0.83)	
Clinical N status				
Negative	43	19 (30.6)	1.00	0.20
Positive	92	25 (21.3)	0.61 (0.31–1.24)	
Histological grade				
1	26	3 (10.3)	1.00	0.06
2–3	109	41 (27.3)	3.26 (0.94–11.35)	
Hormone receptor status				
Negative	42	33 (44.0)	0.15 (0.07–0.33)	<0.01
Positive	93	11 (10.6)	1.00	
ER+/PgR+	68	5 (6.8)		
ER+/PgR−	21	6 (22.2)		
ER−/PgR+	2	2 (50)		

ER estrogen receptor, *pCR* pathological complete response, *PgR* progesterone receptor, *T* tumor size, *T1* (≤2.0 cm), *T2* (2.1–5.0 cm), and *T3* (≥5.1 cm)

[a] Including 3 patients in the P-CEF arm (1 patient with stage IIIC disease and 2 patients who did not undergo breast surgery)

patient in the CP-CEF arm and 3 patients in the P-CEF arm experienced disease progression. All 3 patients in the CP-CEF arm and 10 of 13 patients in the P-CEF arm who experienced disease progression had HR-negative disease.

The pCR rate in the CP-CEF arm was significantly higher than that in the P-CEF arm (31.8 vs. 17.6 %, one-sided $P = 0.01$). Among these pCR patients, 9 of 28 patients in the CP-CEF arm and 4 of 16 patients in the P-CEF arm had DCIS. In the per-protocol population, the difference in pCR rates between the two arms was not significant [28.0 % (14/50) in the CP-CEF arm vs. 24.2 % (15/62) in the P-CEF arm, one-sided $P = 0.179$]. By univariate analysis, treatment arm, clinical tumor size, and HR status were significantly associated with pCR (Table 3), and these were all shown to be independent factors by multivariate analysis. Among HR-negative patients, 23 of 37 patients (61.2 %) in the CP-CEF arm achieved a pCR; this rate was significantly higher than that in the P-CEF arm [26.3 % (10/38), $P = 0.003$, Fig. 3]. Among patients with HR-positive and histological grade 1 disease, 0 of 12 patients in the CP-CEF arm and 1 of 11 patients in the P-CEF arm experienced a pCR. In contrast, among patients with HR-positive and histological grade 2–3 disease, 5 of 39 patients (12.8 %) in the CP-CEF arm and 5 of 42 patients (11.9 %) in the P-CEF arm experienced a pCR. Other factors associated with significantly higher pCR rates in the CP-CEF arm included age (≥50 years), clinical tumor size (T1–2), and histological grade (grade 2–3). After a median follow-up of 12.0 months, 4 and three patients experienced disease recurrence in the CP-CEF and P-CEF arms, respectively.

Safety

Grade 3–4 hematologic toxicities were more common in patients treated with CP than in those treated with P (neutropenia 58.0 vs. 9.9 %, anemia 15.9 vs. 0 %, and thrombocytopenia 1.1 vs. 0 %, respectively, Table 4). Non-hematologic toxicities were similar between the two treatment arms. In the CP-CEF arm, 26 patients discontinued CP due to adverse events, which were predominantly hematologic toxicities [prolonged neutropenia ($n = 19$), febrile neutropenia ($n = 1$), thrombocytopenia ($n = 2$), peripheral sensory neuropathy ($n = 2$), infection ($n = 1$), and elevation of liver transaminase ($n = 1$)], and 3 patients discontinued CEF due to adverse events. Five and six patients in the P-CEF arm discontinued P and CEF, respectively, due to adverse events. One patient in the CP-CEF arm developed acute monocytic leukemia 1.5 years after completion of neoadjuvant chemotherapy.

Discussion

The addition of carboplatin to wPTX followed by CEF significantly improved the pCR rates in the ITT population in the present study. No difference in pCR rates was observed in the per-protocol population, although this could be due to the high rate of discontinuation of neoadjuvant chemotherapy in the CP-CEF arm (37.5 %) and the small sample size.

A meta-analysis of 12 randomized neoadjuvant trials for breast cancer (12,993 patients total) suggested that pCR rates differed by tumor subtype [18]. In patients with HER2-negative and HR-positive disease, the pCR rates of patients with grade 1–2 and 3 were 7 and 16 %, respectively. The pCR rate of patients with TNBC was 34 %. Furthermore, the association between pCR and event-free survival in patients with HR-positive and grade 3 disease or TNBC was significant. In the present study, the difference in pCR rates between the two arms was not significant in patients with HR-positive disease. However, in patients with TNBC, the pCR rate in the CP-CEF arm was

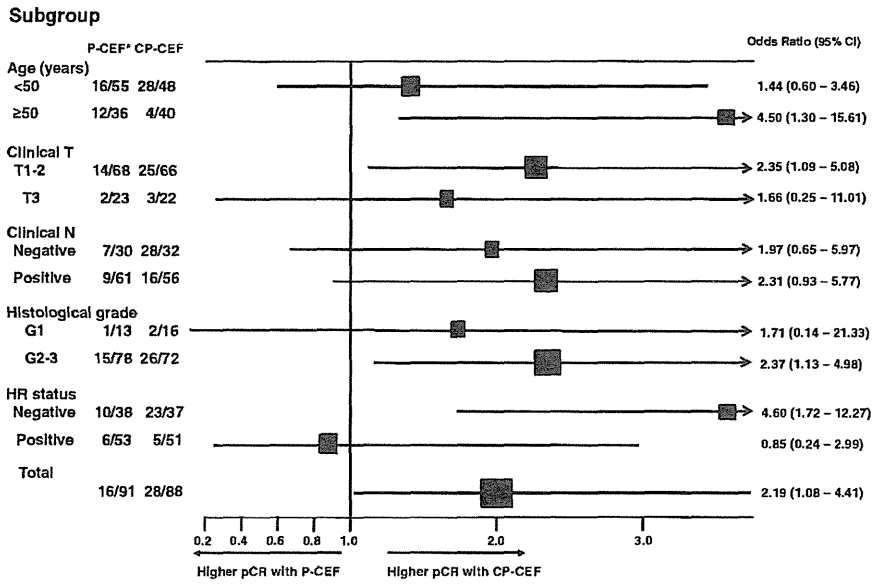

Fig. 3 Odds ratios for pCR rates between the two treatment arms by subgroup. *pCR* pathological complete response, *T* tumor size, *T1* (≤2.0 cm), *T2* (2.1–5.0 cm), and *T3* (≥5.1 cm). *Asterisk* including 3 patients in the P-CEF arm (1 patient with stage IIIC disease and 2 patients who did not undergo breast surgery)

Table 4 Grade 3–4 adverse events (NCI-CTCAE version 4.03)

Treatment arm	CP-CEF				P-CEF			
Adverse events	All		CP phase		All		P phase	
	G3 %	G4 %	G3 %	G4 %	G3 %	G4 %	G3 %	G4 %
Anemia	18.2	1.1	14.8	1.1	1.1	0	0	0
Neutropenia	46.6	19.3	52.3	5.7	17.6	20.9	8.8	1.1
Thrombocytopenia	1.1	0	1.1	0	0	0	0	0
Febrile neutropenia	20.5	0	2.3	0	15.4	0	0	0
Abdominal pain	1.1	0	1.1	0	0	0	0	0
Oral mucositis	1.1	0	0	0	1.1	0	0	0
Nausea	3.4	0	2.3	0	2.2	0	0	0
Vomiting	2.3	0	1.1	0	0	0	0	0
Fatigue	2.3	0	2.3	0	1.1	0	0	0
Infection	4.4	0	2.2	0	1.1	0	0	0
Elevation of ALT	2.3	0	2.3	0	2.2	0	1.1	0
Elevation of AST	1.1	0	1.1	0	1.1	0	1.1	0
Elevation of GGT	1.1	0	1.1	0	0	0	0	0
Anorexia	2.3	0	2.3	0	0	0	0	0
Dehydration	1.1	0	1.1	0	0	0	0	0
Hypertriglyceridemia	1.1	0	1.1	0	0	0	0	0
Hypokalemia	1.1	0	0	0	0	0	0	0
Arthritis	1.1	0	1.1	0	0	0	0	0
Peripheral motor neuropathy	1.1	0	1.1	0	0	0	0	0
Peripheral sensory neuropathy	1.1	0	1.1	0	1.1	0	1.1	0
Syncope	1.1	0	1.1	0	0	0	0	0

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *CP-CEF* carboplatin and weekly paclitaxel followed by cyclophosphamide/epirubicin/5-fluorouracil, *P-CEF* weekly paclitaxel followed by cyclophosphamide/epirubicin/5-fluorouracil, *GGT* gamma-glutamyl transpeptidase, *CP* carboplatin and weekly paclitaxel, and *P* weekly paclitaxel

significantly higher than that in the P-CEF arm (Fig. 3). In the randomized studies of the addition of carboplatin to anthracycline and taxane for TNBC in neoadjuvant settings, one study showed no improvement of the pCR rate by addition of carboplatin (GEICAM/2006-03: $n = 93$, 29.8 vs. 3.48 %, $P = 0.606$) and the other two studies suggested any improvement of the pCR rates (GeparSixto: $n = 315$, 58.7 vs. 37.9 %, $P < 0.05$; CALGB40603: $n = 233$, 60 vs. 46 %, $P < 0.0018$) [19–21]. The present results combined with those of previous studies suggested

an advantage associated with the addition of platinum compounds to anthracyclines and taxanes as neoadjuvant therapy for TNBC.

The dosage and schedule of carboplatin and wPTX in the experimental arm of our study were chosen on the basis of the results of a previous study in advanced ovarian cancer, in which improved survival was observed in patients who received wPTX compared with the conventional triweekly schedule. In that study, 312 patients were treated with carboplatin (AUC of 6 on day 1) plus wPTX (80 mg/m^2 on day 1, 8, and 15) every 3 weeks, and carboplatin doses were reduced for hematologic toxicities in 48 % of patients. Therefore, the AUC of carboplatin in the present study was reduced to 5 [22]. In the present study, hematologic toxicities were more common in the CP-CEF arm, and they resulted in delayed administration or at least one dose reduction of paclitaxel (73.9 %) and dose reduction of carboplatin (20.5 %). In the CALGB 40603 trial, 4 cycles of triweekly administration of carboplatin (AUC6) with wPTX increased grade 3/4 neutropenia and thrombocytopenia [21]. In the 18 weekly administrations of liposomal doxorubicin, paclitaxel, and carboplatin (AUC2) of the GeparSixto study, all treatments were completed by 52.2 % and discontinuations due to adverse events occurred in 37.7 % [20]. The optimum dosage and schedule of carboplatin and wPTX have not yet been established. The frequency of neutropenia in patients who received paclitaxel and carboplatin, which were given every week, was lower than that reported in the present study. A weekly carboplatin and paclitaxel may be an alternative regimen with mild hematologic toxicities. A randomized trial of sequential taxane and anthracycline neoadjuvant regimens showed no significant difference in pCR rates between the two sequences, although the regimen of a taxane followed by an anthracycline was associated with milder hematologic toxicity [23]. In the present study, due to concerns about hematologic toxicities associated with the combination of carboplatin and wPTX, a sequence of a taxane followed by an anthracycline was chosen.

The present study has a number of limitations, and was stopped early before full accrual keeping with 87 % power and one-sided 10 % significance level. In the present study, the definition of HR negativity was <10 % staining of cancer cell nuclei by IHC. Out of concerns about false negative or positive, The ER- and PgR-negativities are recommended <1 % staining of cancer nuclei irrespective of staining intensity with the objectives of clinical trial eligibility for TNBC [24]. In the vitro study, basal-like subtypes of TNBC depending on gene profiles were suggested a highly sensitive to cisplatin, and pragmatic selection method of basal-like subtypes is an issue in the future [15]. The primary endpoint was a pCR rate rather than indicative of long-term outcome. A meta-analysis of neoadjuvant breast cancer trials showed that the magnitude of improvement in pCR did not predict long-term outcomes. However, in patients with TNBC, improvement of pCR was significantly associated with improvement of event-free and overall survival [18]. Therefore, the improvement of pCR associated with the addition of carboplatin in patients with TNBC in the present study may contribute to improved long-term outcomes.

In conclusion, the addition of carboplatin to wPTX followed by CEF for HER2-negative breast cancer improved the pCR rate but resulted in more hematologic toxicity.

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Conflicts of interest MA has declared conflicts related to lecture fees form Kyowa Hakko Kirin Co., Ltd. SO has declared conflicts related to lecture fees from Astra Zeneca K. K., Novartis Pharma K. K., and Chugai Pharmaceutical Co., Ltd. YF has declared conflicts related to conducting research sponsored by Kyowa Hakko Kirin Co., Ltd., Glaxo Smith Kline K. K., Sanofi-Aventis K. K., Daiichi Sankyo Co., Ltd., Taiho Pharmaceutical Co., Ltd., Takeda Bio Development Center Limited, Chugai Pharmaceutical Co., Ltd., Nippon Kayaku Co., Ltd., Nippon Boehringer Ingelheim Co., Ltd., Novartis Pharma K. K., Pfizer Japan Inc., Janssen Pharmaceutical K. K., and Kissei Pharmaceutical Co., Ltd., and remunerations from Astra Zeneca K. K., Eisai Co., Ltd., Ono Pharmaceutical Co., Ltd., Kyowa Hakko Kirin Co., Ltd., Glaxo Smith Kline K. K., Sanofi-Aventis K. K., Daiichi Sankyo Co., Ltd., Takeda Pharmaceutical Co., Ltd., Chugai Pharmaceutical Co., Ltd., Eli Lilly Japan K. K., Nippon Kayaku Co., Ltd., Novartis Pharma K. K., and Bristol-Myers Squibb K. K. All remaining authors have declared no conflicts of interest.

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トピックス
Topics

毎年数多くの新薬が承認されるがん領域で，昨年話題になった薬剤の一つが抗体薬物複合体のトラスツズマブ エムタンシン（別称T-DM1，商品名カドサイラ）でした。抗体医薬と化学療法薬が結合した新たなコンセプトの抗がん剤で，今後乳がん治療に貢献することが期待されています。そこで臨床の第一線で活躍されている原文堅先生に，T-DM1の特徴とこれまでの臨床試験結果についてご解説いただきます。

（編集部）

抗HER2抗体チュブリン重合阻害薬複合体 T-DM1とは？

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はじめに

HER2陽性乳がんは乳がんの約2割を占め，予後不良なサブタイプである。しかし，HER2に対するモノクローナル抗体薬であるトラスツズマブやEGFR/HER2チロシンキナーゼ阻害薬であるラパチニブが登場してから，その予後は大きく改善された。しかしながら，これらの薬剤をもってしても再発，増悪を来す症例は多く，耐性を克服する新規薬剤の開発が課題であった。近年，相次いで新規コンセプトの抗HER2薬剤が開発された。一つはHER2二量体形成阻害薬であるペルツズマブ，もう一つは抗体薬物複合体のT-DM1である。T-DM1は抗体薬であるトラスツズマブの作用と，化学療法薬のDM-1を効率良く細胞内に運ぶ作用をあわせもち，従来の標準治療より効果を高め，毒性を軽減させた薬剤であり，今後の臨床応用が大いに期待できる薬剤である。本稿では，T-DM1の作用機序，臨床試験から得られた結果について述べる。

T-DM1の構造

T-DM1は，抗体薬物複合体という新しい概念で創薬された新規抗HER2治療薬である。T-DM1は，①抗HER2抗体であるトラスツズマブ，②チュブリン重合阻害薬のエムタンシン（DM1），③これらを結びつける安定性の高いリンカー分子のMCC〔N-succinimidyl 4-(N-maleimidomethyl) cyclohexane-1-carboxylate〕――の3つの部分から構成されている[1]（図1）。またDM1はトラスツズマブ1分子に対して，平均3.5分子が結合している。DM1はメイタンシンの誘導化合物であり，メイタンシン自体は植物メイテナス セラタ（*Maytenus serrata*）から単離された薬剤として1970年代にすでに存在していた。前臨床試験で，ビンカアルカロイドの100倍以上，パクリタキセルの24～270倍の殺細胞効果をもつことがわかっていたが[2]，神経毒性や消化管毒性が強く，有効域が極めて狭いため実用には至らなかった。その薬が，抗体薬物複合体という形でHER2陽性乳がんに選択的に作用することで初めて使用可能となった。

T-DM1の作用機序

T-DM1はトラスツズマブと同等の親和性でHER2と結合した後，HER2とT-DM1の複合体としてエンドサイトーシスにより細胞内に速やかに取り込まれ，リソソームにより分解を受けたDM1が細胞内に遊離される。これがチュブリンの重合を阻害し，アポトーシスを誘導す

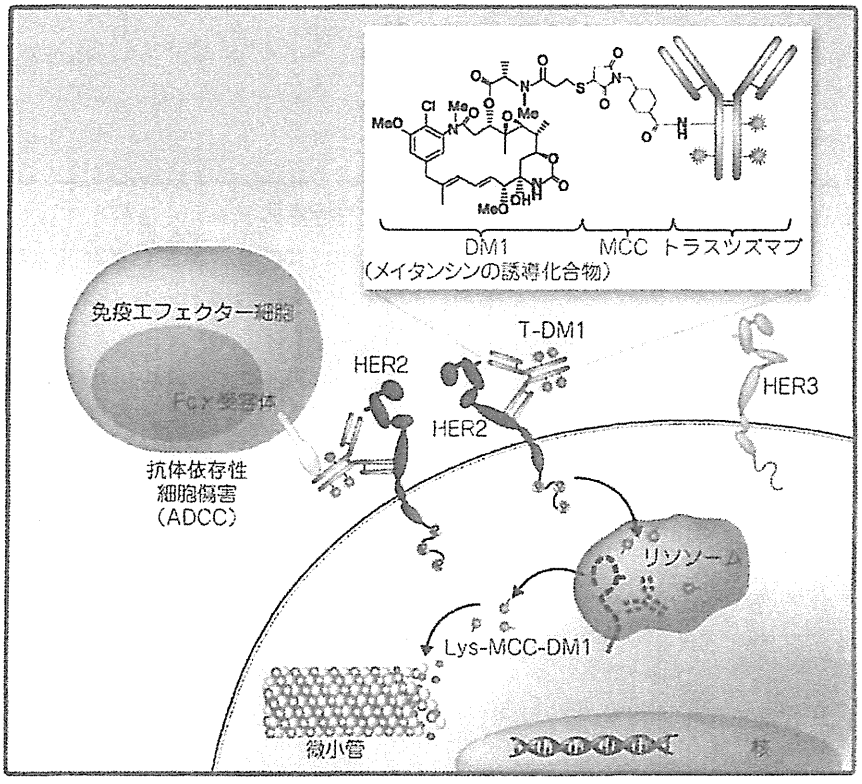

図1　T-DM1の構造と作用機序

〔LoRusso PM. et al : Clin Cancer Res. 17 : 6437-6447. 2011より引用〕

る[3]。また，T-DM1にはトラスツズマブの特性ももっているため，HER2シグナル伝達阻害，HER2細胞外ドメイン切断（shedding）の防止，トラスツズマブのIgG抗体Fcγ部分を介した抗体依存性細胞傷害（ADCC）活性を利用した殺細胞効果を有すると考えられている[4]（図1）。

T-DM1の臨床試験

1．第Ⅰ相試験

トラスツズマブ治療歴のあるHER2陽性進行・再発乳がんの患者を対象に，用量漸増試験として第Ⅰ相試験が行われた[5]。3週ごと投与法4.8mg/kgで用量制限毒性であるグレード4の血小板減少がみられたため，最大耐用量は3.6mg/kgと設定された。3週ごと投与法3.6mg/kgでの有効性（n＝15）はPFS 10.4カ月，臨床的有用率は73%であった。血小板減少以外の有害事象としてはトランスアミナーゼ上昇，悪心，貧血がみられたが，いずれも軽微だった。薬物動態は胆汁排泄で，消失半減期は約3.5日であった。わが国で行われた第Ⅰ相試験（JO2259試験）でも同様の結果が得られ，最大耐用量は3週ごと投与3.6mg/kgとされた[6]。

2．第Ⅱ相試験

化学療法とトラスツズマブの治療歴のあるHER2陽性転移乳がんを対象にT-DM1（3.6mg/kg，3週ごと投与）の単アーム第Ⅱ相試験（n＝112）が行われた[7]。この試験では独立判定，主治医判定で奏効率はそれぞれ25.9%，37.5%であった。また無増悪生存期間（PFS）中央値は4.6カ月の結果が得られた。次いで，トラスツズマブ，ラパチニブ，アントラサイクリン系，タキサン系，カペシタビン既治療歴のあるHER2陽性転移乳がんを対象にT-DM1（3.6mg/kg，3週ごと投与）の単アーム第Ⅱ相試験（n＝110）が行われた[8]。非常に濃厚な前

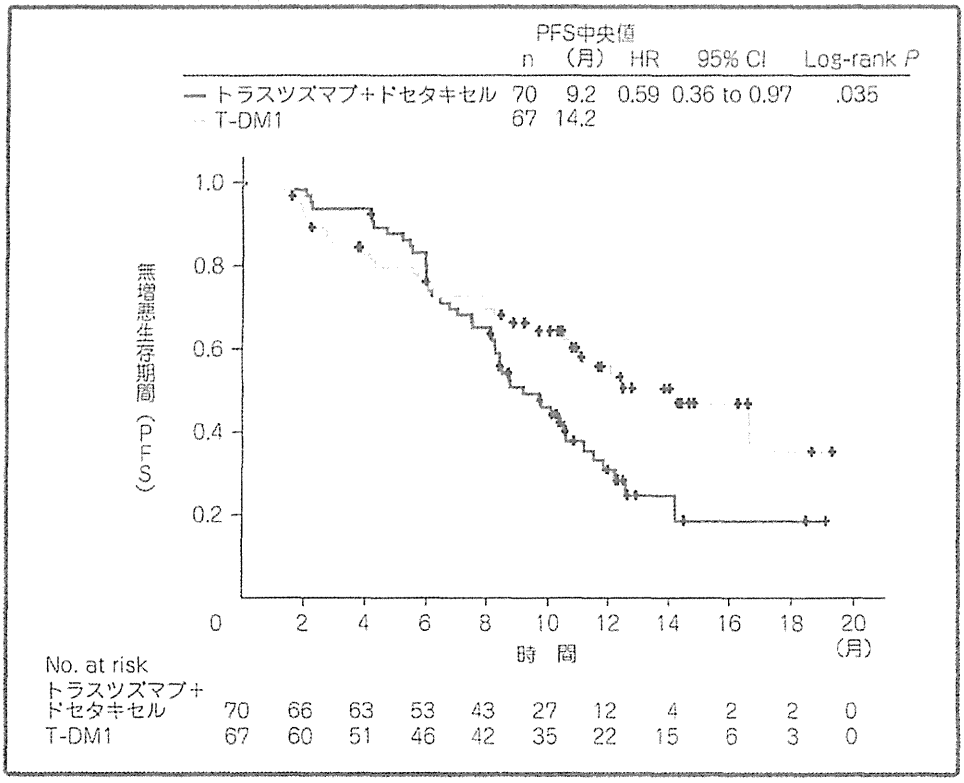

図2　TDM4450g試験における無増悪生存期間の有意な延長

（Hurvitz SA, et al : J Clin Oncol. 31 : 1157-1163. 2013より引用）

治療歴のある患者に対しての投与であったが，奏効率34.5%，臨床的有用率48.2%，PFS中央値は6.9カ月と非常に良好な結果であった。

また，早期治療ラインとして転移性乳がんに対する化学療法歴のないHER2陽性転移性乳がんを対象として，T-DM1とトラスツズマブ＋ドセタキセル併用療法を比較したTDM4450g試験（n＝137）が行われた[9]。主要評価項目は研究者評価によるPFSおよび安全性であった。PFSの中央値はT-DM1群14.2カ月，トラスツズマブ＋ドセタキセル群9.2カ月であり，有意な延長を認めた（HR＝0.59，95%CI：0.364-0.968，P＝0.035）。奏効率はT-DM1群64.2%，トラスツズマブ＋ドセタキセル群58.0%であった（図2）。全生存期間（OS）に関しては，観察期間が短く，死亡イベントが少ないことや，プロトコルで許可されたクロスオーバーによりトラスツズマブ＋ドセタキセル群の50%が病勢進行後にT-DM1治療を受けた交絡により差を認めていない。グレード3以上の有害事象の発生頻度はT-DM1群46.4%，トラスツズマブ＋ドセタキセル群90.9%であった。また，FACT-B-TOI（QOLの評価尺度の一つ）によるQOL悪化までの期間はT-DM1群で有意に長かった（7.5カ月 vs 3.5カ月，HR＝0.58，p＝0.022）。

わが国における第Ⅱ相臨床試験（JO22997試験，n＝73）はHER2陽性転移・再発乳がん（化学療法およびトラスツズマブ既治療）を対象としてシングルアーム試験として行われた[10]。主要評価項目である効果判定委員会評価の奏効率は38.4%（95%CI：27.2-50.5），副次的評価項目のPFS中央値は5.6カ月（95%CI：4.6-8.2）であった。主なグレード3以上の有害事象は血小板減少（21.9%），AST上昇（13.7%），ALT上昇（8.2%），悪心（5.5%）であった。有効性に関しては，海外第Ⅲ相比較試験EMILIA（後述）の結果と遜色なかった。これらの試験結果をもって，2013年11月にわが国でもT-DM1（カドサイラ®）が承認された。しかしながら2014年3月末時

点ではまだ薬価収載に至っていない。

3．第Ⅲ相試験

EMILIA試験は，トラスツズマブおよびタキサン系既治療HER2陽性，切除不能局所進行または転移性乳がん患者を対象に，T-DM1とラパチニブ＋カペシタビン併用と比較したランダム化第Ⅲ相試験（n＝991）である[11]。主要評価項目は独立判定機関によるPFS，OS，安全性であった。局所進行・転移性乳がんに対する治療歴として1レジメン以下の症例は61％であった。

独立判定委員会評価のPFS中央値はT-DM1群で9.6カ月（95％CI：8.25-10.64），ラパチニブ＋カペシタビン群で6.4カ月（95％CI：5.68-7.06），HR 0.650（95％CI：0.549-0.771，層別log-rank検定p＜0.0001）であり（図3），T-DM1群で有意な延長が認められた。OS中央値はT-DM1群で30.9カ月（95％CI：26.81-34.27），ラパチニブ＋カペシタビン群では25.1カ月（95％CI：22.74-27.96），HR 0.682（95％CI：0.548-0.849，層別log-rank検定p＝0.0006）で，事前に設定した早期有効中止基準を満たし，OSの有意な延長が確認された（図4）。奏効率については，T-DM1群で43.6％，ラパチニブ＋カペシタビン群で30.8％とT-DM1群が優れていた（χ^2検定p＜0.001）。また，奏効期間（独立評価）の中央値はT-DM1群で12.6カ月（95％CI：8.4-20.8），ラパチニブ＋カペシタビン群では6.5カ月（95％CI：5.5-7.2）であった。

毒性については，グレード3以上の有害事象の総発現率がT-DM1群で40.8％，ラパチニブ＋カペシタビン群で57.0％と，T-DM1群で低かった。内訳は，T-DM1群のほうが血小板減少症，肝酵素値上昇の発現率が高く，ラパチニブ＋カペシタビン群のほうが下痢，悪心，嘔吐および手足症候群の発現率が高い傾向であった。

副次評価項目である症状無増悪期間はFACT-B-TOIを用いて検討が行われ，症状悪化までの期間の中央値はT-DM1群では7.1カ月（95％CI：5.59-8.44），ラパチニブ＋カペシタビン群では4.6カ月（95％CI：4.14-5.78），HR 0.796（95％CI：0.667-0.951，層別log-rank検定，p＝0.0121）で，T-DM1群で有意に長かった。

第Ⅲ相ランダム化比較試験（TH3RESA試験，n＝602）は，HER2陽性切除不能局所進行もしくは転移性乳がんで，トラスツズマブ，ラパチニブ，タキサン系を含む，2レジメン以上受けた患者が対象である[12]。T-DM1群（3.6mg/kg，3週ごと）と主治医選択治療TPC（treatment physicians' choice）群に2：1の割合でランダム化された。主要評価項目は主治医評価によるPFSとOSであり，副次評価項目は主治医評価による奏効率と安全性であった。病勢進行後はTPC群からT-DM1群へのクロスオーバーが許可されるデザインとなっている。進行・転移性乳がんに対する前治療の中央値は両群とも4レジメンであり，TPC群の治療内容は，抗HER2療法の併用が83.2％，化学療法単独が16.8％であった。併用療法は，トラスツズマブ＋化学療法（68.5％），トラスツズマブ＋ラパチニブ（10.3％），トラスツズマブ＋ホルモン療法（1.6％），ラパチニブ＋化学療法（2.7％）であった。化学療法薬は，ビノレルビンやゲムシタビン，エリブリン，パクリタキセル，ドセタキセルなどが使われた。

PFSの中央値はT-DM1群6.2カ月，TPC群3.3カ月であり，HR 0.528（95％CI：0.422-0.661，p＜0.0001）であった。OSはTPC群の44/198人（22.2％）がT-DM1群へクロスオーバーしたが，OS中央値はT-DM1群では未到達，TPC群は14.9カ月で，HRは0.552（95％CI：0.369-0.826，p＝0.0034）であった。奏効率はT-DM1群で31.3％，TPC群は8.6％であった（95％CI：16.2-29.2，p＜0.0001）。

グレード3以上の有害事象はT-DM1群では32.3％，TPC群は43.5％であった。グレード3以上の有害事象はT-DM1群で血小板減少症，TPC群では好中球減少症，発熱性好中球減少症，下痢であった。

現在進行中の臨床試験

HER2陽性転移・再発乳がんの一次治療として，第Ⅲ相二重盲検無作為化3群比較試験，MARIANNE試験（n＝1,092）が行われている[13]。これは，トラスツズマブ＋タキサン系，T-DM1＋プラセボ，T-DM1＋ペルツズマブ併用の3群を比較する試験で，現在症例集積は終了しており，この結果によりT-DM1が一次治療に組み入れられることが期待される。

その他にも早期HER2陽性乳がんを対象とした周術期

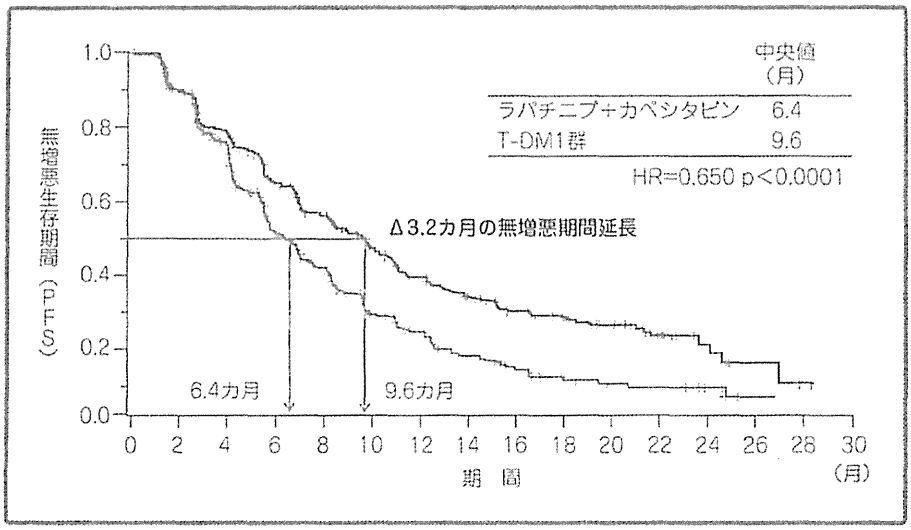

図3　EMILIA試験における無増悪生存期間の有意な延長

〔Verma S. et al : N Engl J Med. 367 : 1783-1791, 2012より引用〕

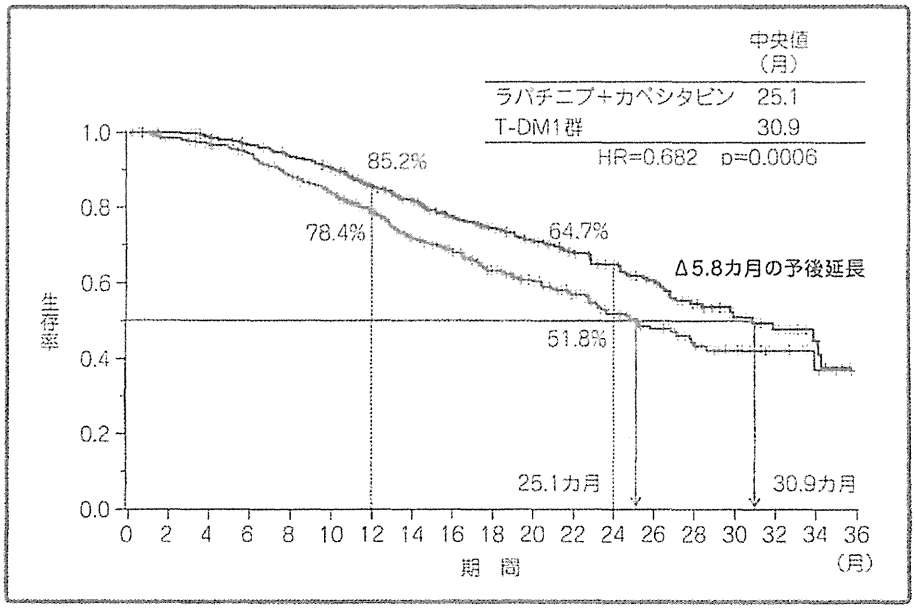

図4　EMILIA試験における全生存期間の有意な延長

〔Verma S. et al : N Engl J Med. 367 : 1783-1791, 2012より引用〕

補助治療の臨床試験が検討されている。術前治療としてはADAPT試験（T-DM1±標準的ホルモン治療 vs トラスツズマブ+標準的ホルモン治療）やKRISTINE（ドセタキセル+カルボプラチン+トラスツズマブ vs ドセタキセル+カルボプラチン+トラスツズマブ+ペルツズマブ vs ドセタキセル+T-DM1 vs ドセタキセル+T-DM1+ペルツズマブ vs T-DM1+ペルツズマブ）が計画されている。また術後治療としては，KATHERINE（術前化学療法で腫瘍の遺残を認めた症例に対して術後治療としてT-DM1とトラスツズマブを比較），ATEMPT（早期HER2陽性乳がん術後治療としてT-DM1単剤とトラスツズマブ+パクリタキセルを比較），KATLIN（HER2

陽性乳がん術後治療としてAC/FECの後に，タキサン系＋トラスツズマブ＋ペルツズマブとT-DM1＋ペルツズマブを比較）などが行われており結果が待たれる。

おわりに

T-DM1は抗体薬物複合体として最も成功した薬剤の一つである。今後は術前・術後の早期の段階での使用や他の薬剤との併用（抗HER2治療薬，ホルモン治療薬，化学療法薬）の試験が実施されることになっており，HER2陽性乳がんの予後は根治が目指せるサブタイプとなることが期待される。

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アブラキサンの臨床での位置づけと今後

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Point

- アブラキサンはパクリタキセルの欠点を補った薬剤であり、前投薬を必須とせず、アルコール過敏症患者にも投与でき、高用量のパクリタキセルを短時間で投与することが可能である。
- CA024試験、CA013試験により、欧米では毎週投与150mg/m^{2}が標準治療とされたが、CALGB40502試験によりover doseであった可能性が指摘され、治験継続性の点で問題視された。
- J0100試験によりアブラキサン260mg/m^2（3週毎投与法）がわが国で承認されたが、アブラキサン毎週投与法の有効性・安全性に関してはランダム化第Ⅱ相比較試験の結果が待たれる。
- アブラキサンの至適投与方法・投与量に関しては議論の余地が残る。わが国ではABROAD試験が計画中であり、海外ではIBCSG42-12/BIG2-12（SNAP試験：NCT01746225）が進行中である。

アブラキサンの特性

アブラキサン（nab-paclitaxel）は、人血清アルブミンにパクリタキセルを結合させた約130nm（ヒト赤血球の約1/100）の均一なナノ粒子性製剤*1であり、従来のパクリタキセルとは異なり、溶媒にポリオキシエチレンヒマシ油や無水エタノールを使用していないため、ステロイドや抗ヒスタミン剤を含む前投薬を必須とせず、アルコール過敏症患者にも投与が可能である。

また、アブラキサンのナノ粒子は、投与後血中で速やかに崩壊し、パクリタキセルが結合した血清アルブミンとなり効率よく腫瘍組織への移行するため、高用量のパクリタキセルを短時間で投与することが可能となっている[1]。

*1…ナノ粒子性製剤

ナノテクノロジーは物質をナノメートルのスケールで制御し、新たな機能を創出する技術である。この技術は創薬にも応用され、リポソーム、高分子ポリマーミセルやアルブミン結合製剤などのナノ粒子製剤が開発されている。これら製剤のメリットは①溶解性が増し、溶解剤が不要となる。②腫瘍組織へ薬剤を選択的、効率的に到達させることで治療効果を高める。などがある。ドキソルビシンをPEG化したリポソームに封入したドキシルやアルブミン結合パクリタキセルであるアブラキサンなどがすでに臨床応用されている。

0910-0474/14/ Y400/ 論文/JCOPY

	アブラキサン(260mg/m²)			従来のパクリタキセル(175mg/m²)			p
	患者/全患者	%	(95%CI)	患者数/全患者	%	(95%CI)	
CRおよびPR							
全患者	76/229	33	(27.09-39.29)	42/225	19	(13.58-2.76)	0.001
一次療法	41/97	42	(32.44-52.10)	24/89	27	(17.75-36.19)	0.029
二次療法以上	35/132	27	(18.98-34.05)	18/136	13	(7.54-18.93)	0.006
アンスラサイクリン前治療							
補助療法および/または転移治療	60/176	34	(27.09-41.09)	32/175	18	(12.56-24.01)	0.002
転移治療のみ	31/115	27	(18.85-35.07)	18/130	14	(7.91-79.78)	0.010
主要な転移部位							
内臓	59/176	34	(26.55-40.50)	34/182	19	(13.02-24.34)	0.002
内臓以外	17/50	34	(20.87-47.13)	8/43	19	(6.97-30.24)	ns
年齢(歳)							
<65	68/199	34	(27.58-40.76)	36/193	19	(13.16-24.15)	<0.001
≧65	8/30	27	(10.84-42.49)	6/32	19	(5.23-32.27)	ns

表1　CA012試験：アブラキサンと従来のパクリタキセルの奏効率(文献2より引用)
ns：統計学的有意差なし。

アブラキサンの臨床試験

CA012試験

転移性乳がん患者おいて、3週ごとパクリタキセル175mg/m²と3週毎アブラキサン260mg/m²の第Ⅲ相比較試験CA012試験(n=460)が行われ[2]、主要評価項目として奏効率と安全性、副次評価項目は、無増悪期間(time to progression：TTP)および全生存期間(overall survival：OS)が評価された。

その結果、奏効率はアブラキサン群33%に対し、パクリタキセル群19%と、アブラキサン群が有意に高かった(p=0.001)。うち一次治療例ではアブラキサン群で42%、パクリタキセル群で27%(p=0.029)、二次治療以降ではそれぞれ27%、13%(p=0.006)であった(表1)。

TTP中央値はアブラキサン群23.0週、パクリタキセル群は16.9週であり、アブラキサン群で有意な延長が認められた(HR 0.75：p=0.006)。

OSに関してはアブラキサン群の値は中央値65.0週、パクリタキセル群は55.7週であり有意な差を認めなかった(p=0.374)が、二次治療以降ではそれぞれ56.4週、46.7週(HR 0.75;p=0.006)と有意差を認めた(図1)。

有害事象はGrade 4の好中球減少頻度がアブラキサン群で有意に低かったが(10% vs. 2%：p<0.001)、末梢神経障害に関してアブラキサン群ではパクリタキセル群と比較し、全Gradeで55.1% vs. 71.2%、Grade 3以上では2.2% vs. 10.5%と高率に認められた。その理由として、アブラキサン群はパクリタキセル群に比べて約1.5倍のパクリタキセル量が投与されているため、蓄積性の末梢神経障害の頻度が高くなったことが示唆されている。

CA024試験

転移・再発乳がんを対象とした4群のランダム化第Ⅱ相比較試験CA024試験(n=302)：アブラキサン3週ごと投与300mg/m²群 vs. アブラキサン毎週投与100mg/m²群 vs. アブラキサン毎週投与150mg/m²群 vs. ドセタキセル3週ごと投与100mg/m²群の結果、アブラキサン毎週投与150mg/m²群はドセタキセル群に比べて無増悪生存期間(progression-free survival：PFS)が有意に長かった(12.9カ月 vs. 7.5カ月、HR 0.75：p=0.006)[3]。

また本試験のUpdate解析では、OSにおいてアブラキサン毎週投与150mg/m²群は33.8カ月、ドセタキセル群