

4. Discussion

Since TOP2A is a target molecule of epirubicin [14], it has been speculated that TOP2A-positive tumors are more sensitive than TOP2A-negative tumors to epirubicin-based regimens. In this connection, *in vitro* studies using various human cancer cell lines have demonstrated that TOP2A-positive cells are indeed more sensitive to doxorubicin than are TOP2A-negative cells [12]. In addition, some studies have been reported with results that demonstrate a significant association between TOP2A expression and clinical response to epirubicin-based regimens in the neoadjuvant setting [11,16]. However, the relationship between TOP2A expression and pathological response has rarely been investigated [39]. pCR appears to be a better marker than clinical response for the evaluation of sensitivity of breast tumors to chemotherapy because pCR is more closely associated with favorable prognosis than is clinical response [33–35]. For our study, we therefore adopted pCR as an endpoint marker for evaluating the response to epirubicin-based regimens. We were able to show a significantly higher pCR rate (17%) for TOP2A-positive tumors than TOP2A-negative tumors (2% pCR), which is consistent with previously reported findings indicating a significant association between TOP2A expression and clinical response [11,16].

Recently, the importance of TOP2A as a predictive factor for epirubicin-based regimens has also been demonstrated in the adjuvant setting. Knoop et al. reported that patients with *TOP2A* gene amplification show an enhanced recurrence-free survival when treated with CEF than they do when treated with cyclophosphamide plus methotrexate plus 5-fluorouracil (CMF), but a similar increase in recurrence-free survival is not seen in patients with a normal *TOP2A* gene [21]. A similar finding has been reported by Tanner et al., who detected a better relapse-free survival for patients with *TOP2A* gene amplification and treated with tailored and dose-escalated FEC than for those treated with low-dose FEC followed by cyclophosphamide plus thiotepa plus carboplatin (CTCb). This difference was not observed in patients with a normal *TOP2A* gene [23]. These studies further support the notion that TOP2A can serve as a predictive marker of sensitivity to epirubicin-based regimens. Both immunohistochemically determined TOP2A protein expression and *TOP2A* gene amplification have reported to be associated with response to epirubi-

cin-based regimens [21,40,41]. Cardoso et al. conducted a comparative analysis of whether TOP2A expression determined by immunohistochemistry or *TOP2A* gene amplification determined by FISH is more closely associated with response to the epirubicin-based regimens, found a stronger association for TOP2A expression [11]. It is further reported that the association between TOP2A overexpression and *TOP2A* gene amplification is not so strong since only 33% of breast tumors with this amplification show TOP2A overexpression, unlike the strong association between HER-2 overexpression and *HER-2* gene amplification [16].

Consistent with previously reported findings [20,42], we found that TOP2A positivity is significantly higher in tumors with a mitotic score of III (67%) or that are ER-negative (49%) or HER-2-positive (59%). Since TOP2A is a key enzyme during cell division and most strongly expressed in the S and G2/M phases [43], TOP2A-positive tumors are thought to have a higher rate of proliferation and a higher proportion of cells in the S or G2/M phases than do TOP2A-negative tumors. It thus seems reasonable to assume that TOP2A-positive tumors are more likely to have a mitotic score of III or to be ER-negative because both types of tumors are highly proliferative. Although HER-2 expression was found to be significantly associated with TOP2A expression, no significant relationship between HER-2 expression and pathological response was observed. In the present study, both Grade 2+ and 3+ were considered to be HER-2 positive but even though HER-2 positive was limited to Grade 3+, we failed to show a significant association of HER-2 status with pathological response (data not shown), indicating that TOP2A rather than HER-2 is a better predictive factor for response to epirubicin-based regimens. Similar results have also been reported [11]. The previously reported association between HER-2 expression and sensitivity to anthracycline-based regimens [3] is thus probably an indirect association mediated through TOP2A.

In addition to the clinical significance of TOP2A, we first investigated that of BRCA1 expression for the prediction of response to epirubicin-based regimens in breast cancers. Although BRCA1 expression alone was not significantly associated with pCR rate, combined analysis of TOP2A and BRCA1 expression was found to be very useful for the prediction of pathological response, i.e., TOP2A-positive and BRCA1-negative tumors showed a pCR rate as high as 30% while other

tumors showed a very low pCR rate of 8% or less. These results seem to suggest that, in addition to TOP2A, BRCA1 modulates sensitivity to epirubicin-based regimens. The exact reason why a lack of BRCA1 expression confers resistance to epirubicin-based regimens is currently unknown but we speculate that DNA double-strand breaks are less likely to be repaired in tumor cells defective in BRCA1 expression, resulting in cell cycle arrest and apoptosis.

In conclusion, we were able to demonstrate that a TOP2A-positive and BRCA1-negative phenotype is predictive of a high sensitivity to epirubicin-based regimens, with a pCR rate of up to 30%. Combined determination of TOP2A and BRCA1 expression by means of immunohistochemistry may be clinically useful for the prediction of tumor response to epirubicin-based regimens. Although TOP2A-positive and BRCA1-negative tumors are generally considered to have a biologically aggressive phenotype leading to a high recurrence rate, our finding seems to suggest that prognosis for such breast tumors, if properly treated with epirubicin-based regimens, could be significantly improved. The dose of epirubicin in the present study appears to be lower than that of a current standard (75 or 100 mg/m²). However, we believe, even in such a lower dose, it is possible to study the association of biomarkers and response to epirubicin-based regimes. But it is possible that higher doses of epirubicin would give the different results though the essential findings are thought not to be affected so much. Our findings, therefore, need to be confirmed by a future study covering a larger number of patients treated with higher doses of epirubicin.

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Phase II study of preoperative sequential FEC and docetaxel predicts of pathological response and disease free survival

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Abstract *Purpose* This multicenter phase II study examined the impact of pathological effect on survival after preoperative chemotherapy in Japanese women with early stage breast cancer. *Patients and methods* Prior to surgery, patients received four cycles of FEC (fluorouracil 500 mg/m², epirubicin 100 mg/m², cyclophosphamide 500 mg/m² q3w) followed by four cycles of docetaxel (75 mg/m² q3w). Primary endpoint was 3 year disease free survival (DFS) stratified by the absence or presence of Quasi-pCR (QpCR; absence of invasive tumor or only

focal residual tumor cells). Secondary endpoints were predictors for QpCR, clinical response, breast conservation rate, and safety. *Results* Between June 2002 and June 2004, 202 women were enrolled. Among 191 assessable patients, 25% achieved QpCR. With 40 months median follow-up, 3 year DFS was estimated at 91% for all patients. 3 year DFS for patients with QpCR was 98% vs. 89% without QpCR (hazard ratio 0.38 [95% Confidence Interval 0.09–0.84], $P = 0.0134$). HER2 status and response to FEC were independent predictors of QpCR. The overall clinical

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response was 75%; 85% of patients achieved breast conservation. Grade 3/4 neutropenia was the most common adverse event, observed in 44% and 35% of patients during FEC and docetaxel, respectively. Treatment related side effects were manageable; there were no treatment related fatalities. **Conclusion** FEC followed by docetaxel is an active and manageable preoperative regimen for women with early stage breast cancer. QpCR following preoperative chemotherapy predicts favorable DFS. HER2 overexpression and clinical response to FEC predict QpCR.

Keywords Clinical trial · Docetaxel · Early stage breast cancer · FEC · Preoperative chemotherapy · Phase II

Introduction

Preoperative systemic chemotherapy has been widely used for patients with operable breast cancer to increase the chance for breast conservation [1–3]. Furthermore, response to preoperative treatment can provide information on long-term survival outcomes. Pathological complete response (pCR) in the breast and axillary lymph nodes predicts a favorable prognosis, whereas non-pCR of the breast or node-positive status does not, which can facilitate tailoring of subsequent treatment [1, 3]. In addition, correlative studies of tumor samples before and after treatment may provide information on markers that could predict response or resistance to treatment [4].

Results from the National Surgical Adjuvant Breast and Bowel Project (NSABP) study B-18 demonstrated the impact of preoperative chemotherapy in patients with operable early stage breast cancer [5]. The protocol-specified anthracycline-containing regimen of four cycles of doxorubicin and cyclophosphamide (AC), resulted in an increased chance of breast-conserving surgery (BCS) compared to no preoperative chemotherapy. The study

established pCR as a prognostic marker for long-term disease-free survival and demonstrated that there was no difference in survival whether chemotherapy was administered before or after surgery. Subsequently, studies such as the Aberdeen trial have demonstrated the benefit of the sequential addition of taxanes to preoperative anthracycline regimens [6, 7]. NSABP Protocol B-27 demonstrated that compared to preoperative AC alone, the addition of sequential docetaxel doubled the pCR rate, increased the clinical complete response (cCR) rate, and increased the proportion of patients with negative axillary nodes [3, 7]. Although NSABP B-27 did not show that the addition of docetaxel to AC significantly improved disease free survival (DFS) and overall survival (OS) compared to AC alone, other studies, mainly of patients with node-positive disease, have shown favorable DFS and OS by including a taxane with an anthracycline, either in sequence or combination [8–12]. Multiple neoadjuvant studies demonstrated that patients with pathological complete response to chemotherapy had a good prognosis [1, 2].

Here we conducted a multicenter prospective neoadjuvant trial with four cycles of fluorouracil, epirubicin, and cyclophosphamide (FEC) followed by four cycles of docetaxel in Japanese patients with operable breast cancer to investigate the relationship between pathological effect and survival. The pathological effect was determined using the definitions of Quasi-pCR (QpCR: complete disappearance of invasive carcinoma in the breast or only focal tumor cells remaining in the stroma in the removed breast) [13]. The primary endpoint was to examine 3 year DFS stratified by pathological response (QpCR versus non-QpCR). We also performed a logistic regression analysis to examine which features were associated with QpCR with this regimen. Clinical response, the rate of BCS, and safety were also evaluated.

Methods

Study design and ethics

This multicenter, open-label, single-arm, phase II clinical study was conducted at 13 institutions throughout Japan. This study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. The protocol was reviewed and approved by the institutional review board of each participating institution and written informed consent was obtained from all patients prior to the study.

Patients

Women aged 20–59 years of age with histologically proven early stage breast cancer (T1c-3 N0 M0/T1-3 N1 M0)

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were enrolled. No prior chemotherapy, radiotherapy, hormonal therapy, or immunotherapy was allowed. Other inclusion criteria were the following: Eastern Cooperative Oncology Group performance status of 0–1; white blood cell count between 4000/mm³ and 12000/mm³; neutrophil count \geq 2000/mm³; platelet count \geq 100000/mm³; hemoglobin \geq 9.5 g/dl; serum bilirubin <1.25 times upper normal limit (UNL), creatinine <1.5 times UNL, or AST and ALT <1.5 times UNL. Patients with congestive heart failure or left ventricular ejection fraction \leq 60% were excluded. Patients were also excluded if they had confirmed infection; serious concomitant illness such as severe cardiovascular disease, uncontrolled diabetes, malignant hypertension and hemorrhagic disease; active concomitant malignancy; brain metastasis; interstitial pneumonia or lung fibrosis confirmed by chest X-ray or computed tomography; pleural or peritoneal effusion that required treatment; pericardial effusion; motor paralysis, peripheral neuropathy or edema history of severe drug allergy; or had previously received long-term corticosteroid therapy. Pregnant or lactating women were also excluded.

Treatment procedures

Four cycles of FEC (fluorouracil 500 mg/m², epirubicin 100 mg/m², and cyclophosphamide 500 mg/m²) administered intravenously (i.v.) on day 1 every 21 days were followed by four cycles of docetaxel i.v. (75 mg/m²) every 21 days, prior to surgery. The doses of docetaxel and epirubicin selected at the time of this study were higher than the approved doses in Japan (60 mg/m² each). Pre-medication consisted of a 5-HT₃ antagonist and dexamethasone i.v. on day 1 with oral dexamethasone on days 2 and 3 with each cycle of FEC and dexamethasone i.v. with or without 5-HT₃ antagonist on day 1 with each cycle of docetaxel. Administration of recombinant human granulocyte colony-stimulating factor (rh G-CSF) and antibiotics was left to the judgment of each investigator. If patients prematurely discontinued FEC treatment, they were expected to proceed to four cycles of docetaxel.

Treatment could be postponed for a maximum of 2 weeks for severe toxicity. If toxicity did not improve during this period, chemotherapy was discontinued and surgery was recommended. Dose reductions of epirubicin from 100 mg/m² to 75 mg/m² and for docetaxel from 75 mg/m² to 60 mg/m² were permitted in case of febrile neutropenia and grade 3 or 4 non-hematological toxicities except for nausea, vomiting, and fatigue. Following chemotherapy and clinical assessment of response, patients underwent surgery. If the tumor was too large or invasive for breast-conserving surgery, modified radical mastectomy was recommended. Sentinel lymph node biopsy

(SNB) was performed to confirm disease stage. Most patients with negative biopsies did not undergo surgical clearance of axillary nodes. Autologous or heterologous reconstructive surgery was performed as needed. All patients who underwent breast-conserving surgery were given standard radiotherapy to the remaining ipsilateral breast tissue after surgical recovery. For patients with node-negative status in the sentinel nodes not requiring axillary dissection, radiotherapy to the axilla was allowed but not required. No recommendations were made for post-study hormone therapy in the protocol.

Assessment

Hormone receptor and HER2 overexpression

Estrogen receptor (ER) status and progesterone receptor (PgR) status were determined by immunohistochemistry at each institute. In general, tumors with >10% positively stained tumor cells were classified positive for ER and PgR. HER2 status was also determined at each institute by immunohistochemistry or by fluorescence in situ hybridization (FISH) analysis. HER2 positive tumors were defined as 3+ on immunohistochemistry staining or as positive by FISH.

Central pathological assessment

Haematoxylin and eosin (H&E) and keratin stained slides were prepared as 5 mm tissue sections from the primary tumor. Pathological breast tumor response was assessed by a central review committee consisting of three pathologists using modified criteria of the Japanese Breast Cancer Society [14]. A blinded central review committee evaluated the pathologic response independently to the local pathologists. In this study, the response of stromal invasion and intraductal component was assessed separately. Cytokeratin immunostaining was performed to confirm residual cancer cells in required cases.

Toxicity and clinical assessment

Toxicity was evaluated according to the National Cancer Institute Common Toxicity Criteria (version 2). Tumor response was assessed using the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines in patients who had measurable lesions. Tumor and toxicity assessments were performed within 4 weeks prior to FEC treatment, after completion of FEC treatment, and before surgery.

Statistical methods

The primary endpoint was to examine 3 year DFS stratified by pathological response (QpCR versus non-QpCR). Secondary endpoints included predictors for QpCR, clinical response, the rate of BCS, and safety.

For the primary efficacy analysis, we assumed that approximately 25% of patients would achieve QpCR and that the 3 year DFS rate in patients with non-QpCR would be 70%. To demonstrate a 20–25% reduction in the hazard of DFS between patients achieving QpCR compared with those without QpCR, we planned to enroll 200 patients. Using the log rank test this would provide $\alpha = 0.05$ and $\beta = 0.2$.

Kaplan–Meier analysis was used to estimate the values of DFS. DFS was compared using a log-rank test stratified for QpCR and non-QpCR. Events for the calculation of DFS include all local, regional, or distant recurrence, all clinically inoperable and residual disease at surgery, all second cancers, contralateral breast cancers, and all deaths.

In the logistic regression analyses, adjustments were made for the stratification variables of menopausal status, tumor size, estrogen receptor status, progesterone receptor status, HER2 status, clinical response to FEC treatment and clinical response to docetaxel following FEC treatment. Analyses were performed with JMP (version 6, SAS Institute Inc.). Analyses of endpoint data reported here are based on information received as of July 2007.

Results

Patient characteristics

Between June 2002 and June 2004, 202 patients were prospectively enrolled. As two patients were ineligible and two patients withdrew consent, 198 patients were assessed for safety. One patient was removed from the study after planned chemotherapy but before surgery because of a protocol violation (non-protocol chemotherapy), four patients elected to not have surgery and withdrew from the study, and two were lost to follow-up, leaving 191 evaluable for clinical, pathologic assessment and DFS.

The median age of the assessable 198 patients was 46 years, and 72% of patients were pre-menopausal. The majority of the patients had T2 tumors (74%), with 20% of the patients having T3 tumors and 6% with T1 tumors (Table 1). Distribution with regard to hormone receptor or HER2 overexpression was representative of that seen in common practice in Japan [15].

Table 1 Patients characteristics ($n = 198$)

	No. of patients	%
<i>Age (years)</i>		
Median	46	
Range	25–60	
<i>Menopausal status</i>		
Pre	142	72
Post	56	28
<i>Tumor stage</i>		
T1	12	6
T2	146	74
T3	40	20
<i>Nodal stage</i>		
N0	80	40
N1	117	59
N2	1	1
<i>Hormone receptor status</i>		
<i>ER</i>		
Positive	133	67
Negative	62	31
Unknown	3	2
<i>PgR</i>		
Positive	100	51
Negative	95	48
Unknown	3	2
<i>HER2 (IHC)</i>		
0	60	30
1+	54	27
2+	42	21
3+	38	19
Unknown	4	2

ER estrogen receptor, PgR progesterone receptor, IHC immunohistochemistry

Percentages may not add up to 100% because of rounding

Compliance to chemotherapy and toxicity

Dose reduction due to toxicities was made in 18% of the patients during FEC treatment; febrile neutropenia (19), grade 3–4 neutropenia without fever (10), suspicion of febrile neutropenia (4), vomiting, and deterioration in liver function (1 each) and 14% of patients during docetaxel therapy, febrile neutropenia (5), grade 3–4 neutropenia without fever (5), neuropathy (2), deterioration in liver function (2), myalgia (2) allergy (1) previous reduction of FEC (8), and unknown (2).

Six patients (3%) discontinued FEC treatment due to toxicities (3: two patients with febrile neutropenia and one with vomiting), progression of disease (2), and mental disorder (1). Ten (please refer toxicity section) patients (5%) discontinued docetaxel treatment due to toxicity (3:

one patient each with rash, febrile neutropenia, and phototoxicity), progression of disease (3), and patients' requests for early surgery (2) changing hospital (1), patient's request (1).

Percentage of treatment cycles requiring dose reduction for FEC, docetaxel and all were 11.1, 11.6 and 11.3%. Percentage of treatment cycles (FEC, docetaxel and all) including rh G-CSF were 10.5, 8.2 and 9.4%, respectively.

The safety profile is summarized in Table 2. Four patients didn't receive docetaxel treatment at patients' request. For toxicity 198 and 194 patients were evaluable for FEC treatment and docetaxel treatment, respectively. The most common adverse event was grade 3 or 4 neutropenia, which was observed in 44% of patients during FEC treatment and 35% of patients during docetaxel treatment. Fever, including febrile neutropenia, was seen in 20% and 7% during treatment with FEC and docetaxel, respectively. The only grade 3–4 non-hematologic toxicities reported were; nausea (12 patients), vomiting (11) and fatigue (3). No fatal events were observed.

Response to treatment

The overall clinical response was 74% (95% CI, 67–80%) with 22% CR and 52% PR. Thirty-eight (51%) of 75 FEC non-responders had a response to docetaxel treatment. One hundred and six of 118 FEC responders maintained their response or had a continued decrease in tumor size with

docetaxel (Table 3). QpCR were seen in 25% of patients (including 16% complete disappearance of invasive carcinoma in the breast). One patient was removed from assessable for BCS because of a protocol violation. BCS was achieved in 85% of all the assessable patients. Ninety-two percent of patients who had original tumor size 3 cm or less underwent BCS; those with larger tumors had an 80% rate of BCS. As of July 11, 2007, with a median follow up of 40 months, the estimated 3-year DFS was 91% for all patients. Patients who achieved QpCR had significantly improved DFS compared to those without QpCR (QpCR (98%) and non-QpCR (89%), log rank test, $P = 0.0333$, Fig. 1). HR 0.38 [95% CI 0.09–0.84], $P = 0.0134$).

Predictive factors of pathological response

A multiple logistic regression analysis was performed to examine which factors among menopausal status, tumor size, estrogen receptor status, progesterone receptor status, HER2 status and clinical response to FEC were associated with QpCR (Table 4). HER2 status and response to the initial FEC treatment and response to docetaxel were independent predictive factors for QpCR. The QpCR rates stratified by HER2 and ER are shown in Fig. 2. QpCR rate was 67, 33, 35 and 13% in HER2 positive/ER negative, HER2 positive/ER positive, HER2 negative/ER negative, HER2 negative/ER positive, respectively.

Table 2 Treatment related toxicities

	FEC (n = 198)		Docetaxel (n = 194)	
	All grades n (%)	Grade 3, 4 n (%)	All grades n (%)	Grade 3, 4 n (%)
<i>Non-hematologic toxicities</i>				
Fatigue	83 (42%)	2 (1%)	83 (42%)	1 (1%)
Diarrhea	17 (9%)	1 (1%)	31 (16%)	0
Nausea	162 (82%)	11 (6%)	81 (42%)	1 (1%)
Vomiting	98 (50%)	10 (5%)	38 (20%)	1 (1%)
Neurotoxicity	6 (3%)	0	85 (44%)	2 (1%)
Constipation	67 (34%)	0	50 (26%)	1 (1%)
Arthralgia/myalgia	12 (6%)	0	60 (30%)	1 (1%)
<i>Hematologic toxicities</i>				
Hemoglobin	119 (60%)	1 (1%)	101 (52%)	0
Platelets	26 (13%)	1 (1%)	3 (2%)	1 (1%)
AST/ALT	81 (41%)	3 (2%)	70 (36%)	1 (1%)
Leukocytes	131 (66%)	68 (35%)	92 (47%)	57 (30%)
Neutrophils	137 (69%)	85 (44%)	85 (44%)	67 (35%)
Febrile neutropenia	–	40 (20%)	–	14 (7%)

FEC fluorouracil, epirubicin, cyclophosphamide

Table 3 Clinical response after FEC and after docetaxel following FEC treatment ($n = 194$)

Clinical response, N (%)	Overall	
	Responder	Non-responder
<i>FEC</i>		
Responder	106 (90%)	13 (10%)
Non-responder	38 (51%)	37 (49%)

cCR + *cPR* responder, *cSD* + *cPD* non-responder, *FEC* fluorouracil, epirubicin, cyclophosphamide, *CI* confidence interval

Discussion

We have presented results from the largest study to date that enrolled Japanese women undergoing preoperative chemotherapy for early stage breast cancer. Our findings demonstrated that four cycles of preoperative FEC followed by four cycles of docetaxel conferred a high rate of BCS, even among patients with primary tumors larger than 3 cm. We found a significant improvement in DFS when QpCR could be achieved, compared to the absence of QpCR. HER2 overexpression, response to FEC and response to docetaxel were significant predictors of QpCR with this regimen.

Regarding toxicity, there were no fatal events and no significant differences in the types and severity of toxicity as compared to other recent studies using similar regimens outside of Japan [6, 8, 9, 16–18]. Compared with overseas studies that also did not allow rh G-CSF the incidence of fever was the same in this study [8, 19]. In another studies which showed lower incidence of febrile neutropenia (13.5%) all patients were treated with rh G-CSF [16].

One of the merits of neoadjuvant chemotherapy for operable breast cancer is to decrease the size of the primary tumor in order to allow for BCS. The study protocol did not provide guidelines for breast conservation; therefore, the

BCS rate that we observed reflected the biases that may occur in real-life clinical practice in Japan. Nevertheless, the BCS rate of 80% that we observed was favorable compared with other neoadjuvant studies performed overseas [3, 16].

The PACS 01 trial which compared six cycles of adjuvant FEC with a sequential regimen of three cycles of FEC followed by three cycles of docetaxel 100 mg/m² (FEC-D) demonstrated an 18% risk reduction in DFS and 27% risk reduction in OS with FEC-D (adjusted $P = 0.017$). This study supports the conclusions that sequential adjuvant chemotherapy with FEC followed by docetaxel significantly improves DFS and OS in node-positive breast cancer patients [9]. In the current study the dose of docetaxel 75 mg/m² was selected based on the recommended doses for docetaxel in Japan, and we showed that the actual 3-year DFS rate of 91% was better than expected based on the results of overseas studies [7, 9, 20]. This confirms that the approved doses of 75 mg/m² is an appropriate does in Japanese women.

Furthermore a new definition of QpCR was defined for pathological effect in this study. When stratified between QpCR and non-QpCR, patients with QpCR had significantly favorable DFS. Indeed by adding docetaxel to FEC patients with QpCR resulted in improved survival similar to previous studies.

Even without anti-HER2 targeting therapy, a QpCR rate >60% was achievable in ER negative and HER2 positive tumors. A multivariate analysis has indicated the significant value of HER2 overexpression, which seems to suggest the importance of HER2 in the prediction of QpCR with this regimen. In this study both an anthracycline and docetaxel were used, so it is not clear which treatment was more strongly associated with HER2 as a predictive value of QpCR. Data in the metastatic and adjuvants setting suggest that docetaxel regimens may be more active than non docetaxel regimens in HER2 positive tumors [8, 21]. The value of HER2 status as a predictor of response to anthracycline-based chemotherapy is still a matter debate. On the other hand, there are several implicative data showing the predictive value of topoisomerase (Topo)-II for anthracyclines because Topo-II is a molecular target of anthracyclines [22–25]. There is evidence that HER2 amplification and Topo-II amplification usually occur in parallel and it is rare to have Topo-II amplification without HER2 amplification [23, 26]. In this study QpCR rate might clarify the difference between HER2 positive tumors and HER2 negative tumors. No patient has received trastuzumab in the adjuvant setting. Future translational studies will be necessary to explore the significance of Topo-II amplifications as well as HER2 gene amplifications in the prediction of the pathological response of this regimen. This result will be included the information in the future if

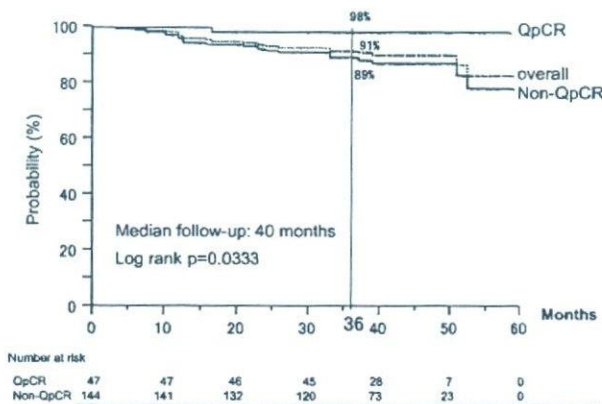
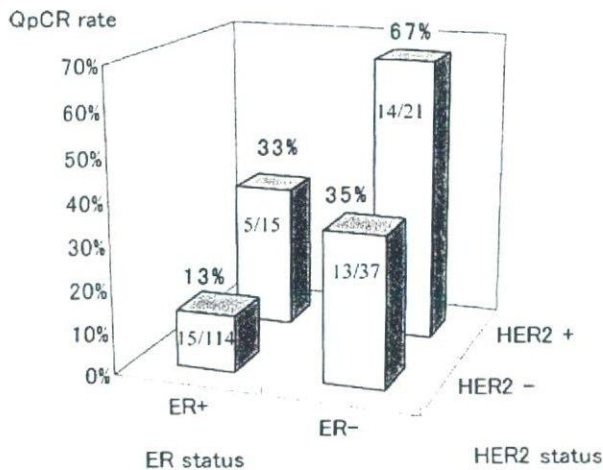


Fig. 1 Relationship of QpCR and non-QpCR to disease free survival

Table 4 Predictive variables for QpCR

Variables	Before treatment	After FEC treatment	After docetaxel following FEC treatment
	OR 95% CI (P)	OR 95% CI (P)	OR 95% CI (P)
<i>Menopausal status</i>	1.43	1.38	1.37
Pre (versus post)	0.94–2.15 (NS)	0.89–2.14 (NS)	0.87–2.12 (NS)
<i>Tumor size</i>	0.89	0.93	0.87
>3 cm (vs ≤3 cm)	0.61–1.3 (NS)	0.63–1.37 (NS)	0.59–1.28 (NS)
<i>ER</i>	1.4	1.44	1.35
Negative (versus Positive)	0.87–2.27 (NS)	0.88–2.36 (NS)	0.81–2.23 (NS)
<i>PgR</i>	1.61	1.49	1.65
Negative (versus Positive)	0.97–2.67 (NS)	0.89–2.51 (NS)	0.98–2.79 (NS)
<i>HER2</i>	2.02	2.24	2.11
3+ (vs <3+)	1.31–3.11 (0.0014)	1.42–3.53 (0.0005)	1.36–3.3 (0.0009)
<i>Clinical response to FEC treatment</i>	–	1.78	–
Response (versus non-response)	–	1.15–2.76 (0.0096)	–
<i>Clinical response to docetaxel following FEC treatment</i>	–	–	1.99
Response (versus non-response)	–	–	1.14–3.47 (0.0154)

QpCR quasi pathological complete response, FEC fluorouracil, epirubicin, cyclophosphamide, OR odds ratio, ER estrogen receptor, PgR progesterone receptor, CI confidence interval, NS not significant

**Fig. 2** Relationship between QpCR and HER2/ER status ($n=187$)

we use anthracycline and trastuzumab for all HER2 positive patients.

In the present study, though a multivariate analysis hasn't indicated the significant value of the status of hormone receptor, QpCR rate was higher in ER negative tumors than ER positive tumors, and QpCR rate in ER negative and HER2 positive tumors was remarkably high compared with ER positive and HER2 negative tumors. This model suggests that ER status is a dependent predictor, for QpCR possibly because it is related to HER2 expression. The sample size was perhaps too small to effectively determine the true impact of ER negative status

as a predictor of QpCR. As most patients who are HER2 positive are also ER negative, it is likely that ER status will have some predictive value. However, larger studies are needed to determine this. These results are important for considering individual preoperative systemic therapy. This trend was similar to previous studies using AC followed by paclitaxel regimens, though the therapeutic situations are different [10, 12, 27, 28]. According to recent meta-analyses of post-operative adjuvant therapy, chemotherapy including cyclophosphamide/methotrexate/5FU (CMF)-type regimens, anthracycline-containing regimens and anthracycline followed by paclitaxel are more effective for hormone receptor negative tumors than for hormone receptor positive tumors [10–12, 27–32]. However, while hormone receptor negative tumors may be more responsive to preoperative regimens, a survival benefit can be observed regardless of receptor status [2]. In this study a multivariate analysis hasn't indicated the significant value of the status of hormone receptor. This may be affected by addition of docetaxel. Dose response with anthracycline is also different between hormone receptor positive tumors and hormone receptor negative tumors. For ER negative tumors, higher anthracycline doses may be required for improved prognosis, however, for ER positive tumors it might not be necessary [29].

In this study, most tumors responded to docetaxel even if they did not respond to FEC. However, some tumors showed a response to the initial therapy but a lesser response to the second therapy. This underscores the need to include non-cross resistant treatments in the

management of early stage breast cancer [33]. Various non-cross resistance molecules may be involved in this clinical phenomenon. Recent investigations indicate that initial chemotherapy may change the phenotype of the tumor by inducing pro-survival molecules in tumor cells or stroma [2, 3, 5, 7, 16]. In particular, key mediators such as nuclear factor-kappa B, cyclooxygenase-2 and thymidine phosphorylase are known to be induced by chemotherapy frequently, which may change those tumors relatively anti-apoptotic to the second chemotherapy [34–36]. From the clinical point of view, it would be useful to modify the treatment schedule based on initial response to treatment. Since the types of pro-tumor molecules and the magnitude of induction are different between agents, it might be reasonable to consider a different sequence (taxane followed by anthracycline), if information on the tumor phenotype could be obtained before starting treatment. Various treatment scenarios for non-responders to FEC could be considered. According to recent study results, surgery might be an option for non-responders to initial anthracyclines [37]. In order to enhance the effect of docetaxel, the combination with fluoropyrimidines such as capecitabine may be an option. Obviously for HER2 overexpressing tumors, anti-HER2 containing therapy should be considered. For the ER positive and HER2 negative phenotype, hormone therapy might be an option if tumors are relatively well differentiated. Individual treatment based on ER/HER2 status and the clinical response to the initial anthracyclines may be integrated as future direction [37].

In conclusion, 8-cycle preoperative chemotherapy with non-cross resistant regimens, FEC followed by docetaxel, is safe, feasible, and effective as primary systemic therapy for women with early stage breast cancer. In particular, the regimen allows a majority of Japanese patients to avoid the need for mastectomy. Patients with QpCR demonstrated significantly superior survival results. HER2 over-expression, response to FEC and response to docetaxel were significant predictors for QpCR. Based on our results, preoperative FEC followed by docetaxel should be considered a standard option for the treatment of Japanese women with operable breast cancer.

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原著

2008.2.1受付

原発乳癌に対するFEC followed by docetaxel 100mg/m² 併用療法による術前化学療法の検討—JBCRG02—

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JBCRG conducted a multicenter prospective neoadjuvant trial with 4 cycles of FEC followed by 4 cycles of docetaxel 100 mg/m² in women with primary operable breast cancer to evaluate efficacy and safety. Between August 2004 and July 2006, 50 patients were enrolled. Pathological complete response (pCR) as primary endpoint was 27%. Quasi-pCR was 31% giving an overall clinical response of 67%, with breast conservation surgery rate of 82%. 84% of patients completed 8 cycles of chemotherapy and 52% of patients completed all cycles without dose reduction. The common adverse events during docetaxel treatment were grade 3 diarrhea, neurotoxicity, edema, myalgia and arthralgia, which responded to appropriate supportive care. Preoperative FEC followed by docetaxel 100mg/m² for primary operable breast cancer was effective and tolerated with appropriate supportive care and reduction for Japanese patients.

Key words : Primary systemic chemotherapy, Clinical trial, FEC, Docetaxel

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はじめに

乳癌治療においては、手術とならび放射線治療

や、ホルモン療法、epirubicinなどアンスラサイクリン系薬剤とdocetaxelなどタキサン系薬剤などの化学療法、さらに分子標的薬剤などを組み合わせた薬物治療が行われている。転移・再発乳癌に対する治療の目的は、生存期間の延長、症状緩和によるQOLの改善であり、患者の状態をみながら治療方針を決定していくことが重要である。一方、原発乳癌に対する薬物療法の目的は、全身治療による再発予防であり、根治を目指し早期に全身治療を行うことで再発や死亡リスクを軽減させることが海外の多くの臨床試験から証明されている¹⁾。

Wolmarkらは、doxorubicin/cyclophos-

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phamide (AC) を用い、術前化学療法と術後化学療法の比較したNSABP B-18において、生存に関して両群に差は認められず、術前化学療法により pathological complete response (pCR) が得られた症例のみ生存期間、無病生存期間ともに明らかな予後の改善が認められたことを報告した²⁾。この試験以降、術前化学療法では、薬剤の感受性を直接知ることができ、ある程度の予後予測ができること、down stagingにより乳房温存の適応が拡大することなどが明らかになり、多くの術前化学療法試験が行われてきている。

また、NSABP B-27では、Bearらは、術前化学療法においてAC 4コースにdocetaxel 100mg/m²を4コース逐次投与追加した群 (AC-docetaxel) がAC単独群と比較し、有意にpCR率が高い結果が得られたことを報告した³⁾。

われわれJapan Breast Cancer Research Group (JBCRG) ではアンシラサイクリン系薬剤としてdoxorubicinよりも心毒性が少ないepirubicinを、タキサン系薬剤としてdocetaxel 75mg/m²を選択し、原発乳癌に対するfluorouracil 500mg/m²/epirubicin 100mg/m²/cyclophosphamide 500mg/m² (FEC) followed by docetaxel 75mg/m²併用療法による術前化学療法 (FEC-DOC75) を検討するJBCRG01試験を行い、pCRや臨床効果などの有効性と安全性を確認した⁴⁾。そこで次の段階として、docetaxelの用量を海外における原発乳癌に対して使用されている100mg/m²にすることにより、原発乳癌に対しより高いpCRが得られることを期待し、primary endpointを病理組織学効果として原発乳癌に対するFEC followed by docetaxel 100mg/m²併用療法による術前化学療法 (FEC-DOC100) を検討するJBCRG02試験を行った。

1. 対象と方法

1) 試験の目的

切除可能な原発乳癌症例 (T1c-3N0M0/T1-3N1M0) を対象に、FEC 4コース投与後docetaxel 100mg/m²を4コース投与する併用療法による術前化学療法を行い、有効性と安全性を検討した。

Primary endpointは病理組織学的効果、second-

dary endpointは安全性 (有害事象、治療完遂率)、抗腫瘍効果、乳房温存術施行率とした。

2) 対象症例

切除可能な原発性乳癌症例 (T1c-3N0M0/T1-3N1M0) のうち、以下の基準を満たす症例を対象とした。①組織学的に浸潤性乳癌と診断された症例、②前治療として化学療法、放射線療法、内分泌療法、免疫療法が行われていない症例、③Performance Status (P.S.) が0～1の症例、④測定可能病変を有する症例、⑤主要臓器の機能が十分に保持されており、以下の基準を満たす症例。ヘモグロビン9.5g/dL以上、白血球数4,000/mm³以上、12,000/mm³以下、好中球数2,000/mm³以上、血小板数100,000/mm³以上、血清総ビリルビン値施設基準値上限の1.25倍以下、AST、ALT施設基準値上限の1.5倍以下、血清クレアチニン値施設基準値上限の1.5倍以下、ejection fraction 60%以上、心電図正常。⑥年齢20歳以上60歳未満の症例、⑦本試験の参加について被験者本人の同意が文書にて得られた症例。

なお以下の基準に該当した場合は除外した。①薬剤過敏症の既往歴のある症例、②重篤な合併症を有する症例 (例えば、悪性高血圧、うっ血性心不全、冠不全、6カ月以内の心筋梗塞、治療を要する不整脈、感染症、出血傾向の発現等)、③発熱を有し、感染の疑われる症例、④末梢神経症状を有する症例、⑤治療を要する胸水・心嚢水貯留例、⑥活動性の重複癌を有する症例、⑦炎症性乳癌症例、⑧両側乳癌の症例、⑨男子乳癌の症例、⑩妊婦、授乳婦および妊娠の可能性 (意志) のある女性、⑪浮腫のある症例、⑫水痘症の症例、⑬胸部単純X線写真およびCTで明らかな間質性肺炎、または肺線維症のある症例、⑭あらかじめステロイドの治療を必要とする症例、⑮精神疾患既往、または治療中の症例、⑯その他、試験責任医師が不適当と判断した症例。

3) 投与方法

選択基準を満たす切除可能な原発乳癌患者に対してFEC (fluorouracil 500mg/m², epirubicin 100mg/m², cyclophosphamide 500mg/m²) を3週間

間隔で4コース施行後, docetaxel 100mg/m²を3週間間隔4コース施行し, 3~6週後に手術を行うこととした。いずれもPDと判定されない限り4コース投与することとした。

4) 2コース目以降の投与基準

2コース目以降の投与時に, 投与開始前に以下の基準を満たしていることを確認し開始することとした。これらの基準を満たさない場合には, 1~2週ごとに経過を観察し, すべて満たした場合に次コースの投与を開始した。

①好中球>2,000/mm³ 血小板>100,000/mm³

G-CSFの投与を行った場合は投与終了後3日以上観察期間を設けて, この基準を満たしていることを確認する。

②末梢神経障害, 浮腫: Grade2以下

③末梢神経障害, 浮腫, 脱毛以外の非血液毒性: Grade1以下

5) 2コース目以降の減量基準

前コース中に下記の有害事象が認められた場合にはepirubicin, docetaxelをそれぞれ25%減量してもよいこととした。一度減量した場合は, 減量した投与量で継続投与し, 減量後下記の有害事象が再度観察された場合には中止してもよいこととした。

その他, 試験担当医師の判断により必要と考えられた場合も, 減量もしくは中止することとした。

(1) 発熱性好中球減少が認められた場合

好中球数1,000/mm³未満, 腋窩で38°C(舌下で38.5°C)以上の発熱が認められた場合。ただし, 好中球数の測定は必須とせず, day4からday18の期間に38°C以上の発熱が認められた場合は, 時期と発熱の程度からGrade3以上の発熱性好中球減少と判断することとした。

(2) 脱毛, 悪心, 嘔吐, 全身倦怠感を除くGrade3以上非血液学的毒性が認められた場合

6) 治療期間中の併用療法および支持療法

本試験の評価に影響を及ぼすと考えられる治療(他の抗悪性腫瘍剤, ホルモン療法, biochemical modulation, 放射線療法および手術療法, ビスホ

スフォネート製剤等)の併用は治療期間中は禁止することとした。各コースのpremedicationは各施設の判断にて行うこととした。出現する有害事象に対しては治療を適宜行い, 実施した場合は対症療法を症例報告書に記載することとした。

7) 評価方法

病理組織学的効果は病理中央判定会を実施し「乳癌の組織学的効果判定基準(日本乳癌学会/編乳癌取扱い規約 第15版)」⁵⁾を基にしたJBCRGの基準⁶⁾により評価を行った。浸潤巣のGrade3をpCR, 完全奏効に非常に近い効果があるがごく少量の癌細胞の残存をnear pCRとし, pCRにnear pCRを加えた場合をQuasi-pCR (QpCR)とした。

有害事象のGradeは, NCI-Common Toxicity Criteria Ver.2.0の日本語訳JCOG版⁷⁾に基づいて評価した。抗腫瘍効果は固形がんの治療効果判定のための新ガイドライン(RECISTガイドライン)⁸⁾に従い評価することとした。

8) 症例数の設定根拠

本試験のpCR率が, FEC-DOC75の中間集計時のpCR率⁹⁾と比較し15%上昇すると仮定し, 期待値29%, 閾値14%とした場合, α エラー5%, β エラー20%にて二項分布に基づいて算出すると, 必要症例数は46例となる。脱落例などを考慮して, 本試験の目標症例数を50例と設定した。

9) 試験の承認

本試験を実施する前に, 施設内審査委員会あるいは倫理委員会に実施試験計画書, 患者同意説明文・同意書を提出し許可を得ることとした。

3. 結果

1) 解析対象

2004年8月から2006年7月までに50例が中央登録方式にて登録された。病理組織学的効果, 抗腫瘍効果, 乳房温存術施行率は, 中央病理判定にて非浸潤癌と判定された2例とプロトコール規定外の治療を施行した3例を除く45例, 安全性(有害事象, 治療完遂率)は50例で解析を行った。Docetaxelの有害事象は, 未投与の3例を除き評

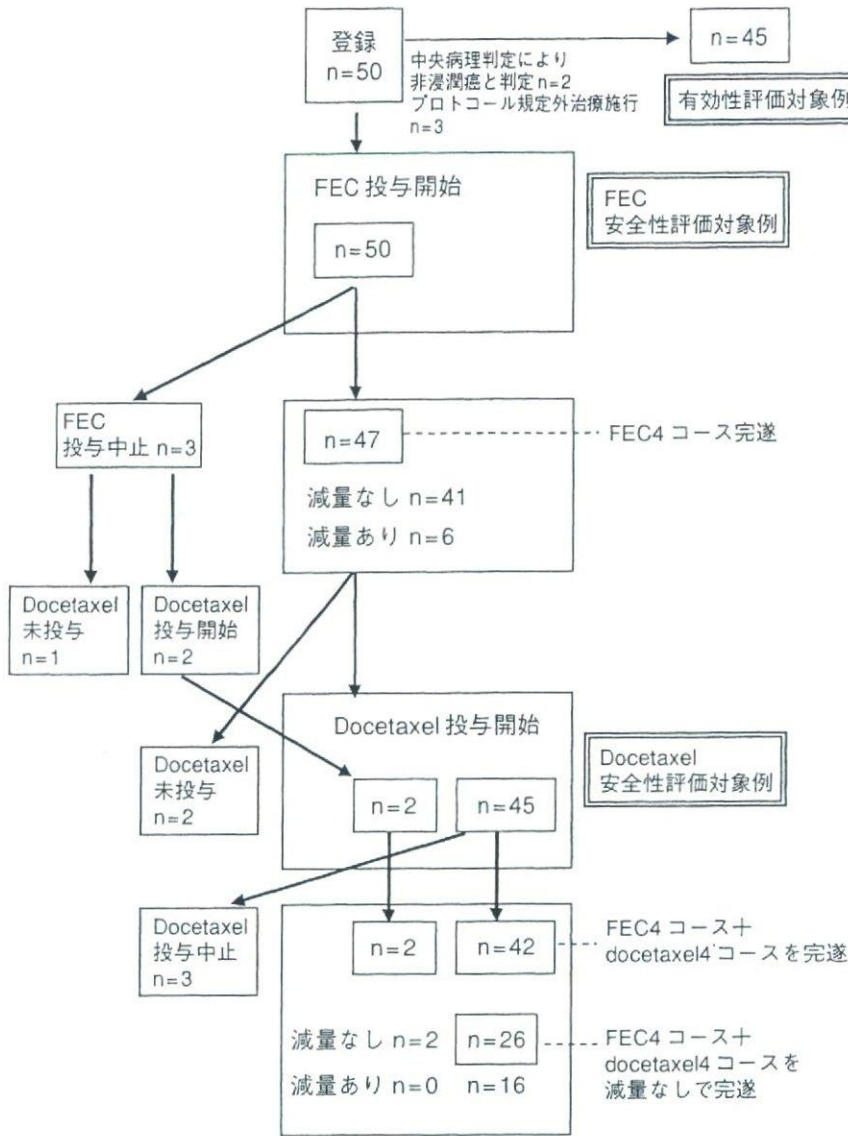


図1 投与状況及び症例の取扱い

価した (図1)。

2) 対象症例の背景因子

表1に患者背景を示す。年齢は中央値47歳(30~58歳)であり、治療開始時の全身状態は全例PS0であった。閉経状況は閉経前39例、閉経後11例であった。腫瘍径の中央値は35mm(10~130mm)、TNM分類は、T1:6例、T2:36例、T3:8例、N0:16例、N1:34例であり、41例がStageIIであった。ホルモン受容体については、ER陽性:31例、ER陰性:16例、不明:3例、PgR陽性:21例、PgR陰性:25例、不明:4例であった。HER2の発現状況は、免疫組織染色法(IHC法)によるスコア0:10例、1+:13例、2+:11例、3+:12例、不明:4例であった(表1)。

3) 有効性

(1) 病理組織学的効果

病理組織学的効果はpCRが27%(12/45)[95%信頼区間(CI)15~42%]であった。pCRとnear pCRを含めたQuasi-pCR(QpCR)は31%(14/45)であった(図2)。ER・HER2 status別によるpCRは、ER陽性では21%(6/29)、ER陰性では38%(5/13)、HER2陽性(3+)では56%(5/9)、HER2陰性では22%(7/32)であった。

(2) 抗腫瘍効果

FEC投与後の臨床効果はCR 4例、PR 20例、SD 19例、PD 1例、NE 1例であり、抗腫瘍効果は53%(24/45)であった。一方、docetaxel投与後の臨床効果はCR 13例、PR 17例、SD 10例、PD 1例、NE 4例となり、抗腫瘍効果は67%(30/45)

表1 患者背景

		患者数	(%)	
年齢(歳)	中央値	47		
	範囲	30~58		
PS	0	50	(100)	
	1	0	(0)	
閉経状況	前	39	(78)	
	後	11	(22)	
腫瘍径(mm)	中央値	35		
	範囲	10~130		
T分類	T1	6	(12)	
	T2	36	(72)	
	T3	8	(16)	
N分類	N0	16	(32)	
	N1	34	(68)	
病期	StageI	1	(2)	
	StageIIA	19	(38)	
	StageIIB	22	(44)	
	StageIII	8	(16)	
ホルモン受容体	ER	+	31	(62)
		-	16	(32)
		不明	3	(6)
	PgR	+	21	(42)
		-	25	(50)
		不明	4	(8)
HER2	0	10	(20)	
	1+	13	(26)	
	2+	11	(22)	
	3+	12	(24)	
	不明	4	(8)	

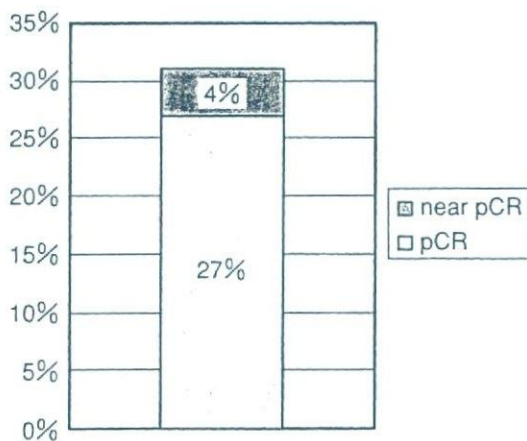


図2 病理組織学的効果

[95%CI 51~80%]であった。

(3) 乳房温存術施行率

37例が乳房温存術を施行し、乳房温存術施行率は82% (37/45)であった。

4) 安全性 (有害事象と治療完遂率)

(1) 有害事象

有害事象を表2に示す。Grade3以上の血液毒性として、FEC投与中、docetaxel投与中ともに白血球減少 (FEC投与中 6%, docetaxel投与中 11%:以下この順)、好中球減少 (12%, 13%)、発熱性好中球減少 (2%, 2%)が認められた。

FEC投与中Grade3以上の非血液毒性は、悪心 (4%), 嘔吐 (6%), 食欲不振 (2%), 便秘 (8%)が認められた。Docetaxel投与中では、Grade3以上の悪心 (2%), 食欲不振 (2%), 下痢 (6%), 便秘 (2%), 知覚性神経障害 (6%), 浮腫 (2%), 筋肉痛 (11%), 関節痛 (6%)が認められた。Grade1, 2を含むと筋肉痛は55%, 関節痛は57%に認められ、減量する症例が6例あり、1例は投与を中止した。また、浮腫は68%に、知覚性神経障害は74%に認められたが、これらの副作用で減量や投与を中止した症例はなかった。

(2) 投与状況及び治療完遂率

投与状況については、84% (42/50)は8コースを完遂した。減量を行わず8コースの予定投与量を施行されたのは52% (26/50)であった。(図1)ただし、FEC施行中の有害事象によりFEC施行中に減量した6例は、docetaxel 1コース目から75mg/m²で投与を開始した。

4. 考察

FEC followed by docetaxel 75mg/m²を投与したJBCRG01試験 (FEC-DOC75)と本試験を比較すると、臨床効果は74%と68%、乳房温存率は85%と82%とほぼ同様であったが、pCR rateは16%と27%であった。これはdocetaxel 100mg/m²を投与したNSABP B-27のpCR 26%と同様の結果であり、docetaxelを75mg/m²から100mg/m²に増量することによって得られた可能性がある。この結果から、わが国においても海外のdocetaxel 100mg/m²を使用した試験と同等のpCRが得られることが示唆された。

一方、docetaxelの血中濃度には個人差があり、1コース目のAUCが血液毒性の重要な予測因子であることなどが報告されている¹⁰⁾。しかし、血中濃度測定は一般的ではなく、本試験においても患

表2 有害事象

	FEC (n=50)		Docetaxel (n=47)					
	Grade3/4		Grade1-4					
	n	%	n	%				
血液毒性								
白血球減少	3	6	33	66	5	11	12	26
好中球減少	6	12	19	38	6	13	7	15
発熱性好中球減少	1	2	1	2	1	2	1	2
ヘモグロビン減少	0	0	19	38	0	0	23	49
血小板減少	0	0	2	4	0	0	0	0
AST	0	0	13	26	0	0	15	32
ALT	0	0	19	38	0	0	12	26
クレアチニン	0	0	1	2	0	0	0	0
非血液毒性								
疲労	0	0	37	74	0	0	33	70
悪心	2	4	44	88	1	2	20	43
嘔吐	3	6	29	58	0	0	6	13
食欲不振	1	2	25	50	1	2	19	40
味覚異常	0	0	25	50	0	0	34	72
口内炎	0	0	34	68	0	0	23	49
便秘	4	8	33	66	1	2	18	38
下痢	0	0	17	34	3	6	15	32
血管炎	0	0	13	26	0	0	4	9
頭痛	0	0	7	14	0	0	4	8
色素沈着	0	0	6	12	0	0	0	0
めまい	0	0	5	10	0	0	2	4
アレルギー	0	0	4	8	0	0	4	9
神経障害(知覚性)	0	0	9	18	3	6	35	74
神経障害(運動性)	0	0	0	0	0	0	1	2
浮腫	0	0	10	20	1	2	32	68
筋肉痛	0	0	5	10	5	11	26	55
関節痛	0	0	3	6	3	6	27	57
皮膚の乾燥	0	0	26	52	0	0	27	57
爪の変化	0	0	1	2	0	0	8	17
流涙	0	0	0	0	0	0	7	15
体重増加	0	0	3	6	0	0	8	17
体重減少	0	0	0	0	0	0	2	4
脱毛	—	—	48	96	—	—	46	98

者個人の有害事象の発現に注意しながら投与を施行し、支持療法や患者指導についても工夫が必要と考えられた。

われわれJBCRGの試験ではとくに、支持療法や患者指導についてはプロトコルで規定していなかった。しかし以前から、参加施設の支持療法を施設間で共有する方法を模索してきた。その一環として、各参加施設が支持療法をどのように工夫されているかを調査する目的で、アンケートを実施した¹¹⁾。その結果、得られた支持療法の工夫を共有化することによって治療効果を最大化し、さらに外来ベースで薬物療法を管理できるようになってきた。

本試験では、Grade3の下痢、悪心、便秘、食欲不振、知覚性神経障害、浮腫、筋肉痛、関節痛が認められた。これらの中で悪心・嘔吐、便秘などは、JBCRG内で共有化している支持療法や患者指導により対応することができた¹¹⁾。一方、Grade3の発現頻度が増えた有害事象をFEC-DOC75と本試験で比較すると、下痢(FEC-DOC75 1%, FEC-DOC100 6%:以下この順)、知覚性神経障害(1%, 6%), 筋肉痛(1%, 11%), 関節痛(1%, 6%)であった。とくにその中でdocetaxel 100 mg/m²投与中に筋肉痛・関節痛により減量する症例が6例あり、1例は投与中止に至ったことが、試験実施中の中間解析により判明した。そこでその後は、NSAIDsなどの鎮痛薬を事前に処方し、早期に使用することを推奨することにより、以後は筋肉痛・関節痛により減量や中止する症例はなくなった。これらもJBCRG内で共有化している支持療法や患者指導を行った結果と考えられる。

その他、半数近くの患者で発現している口内炎、浮腫、神経障害、爪の変化を含む皮膚の症状に対しては現在確立した標準的な治療法はない。本試験の一部の参加施設(聖路加国際病院)では、患者指導を行い治療前とは異なる症状が現れた場合には予定された外来受診日以外にも連絡をもらい、必要な際には早期に支持療法を行い対処している。とくに、浮腫に対しては、水や塩分の過剰摂取への注意喚起、日々の体重測定、マッサージを勧める、また、皮膚症状に対しては、爪の剥離時に浸出液がないか悪臭がないかを確認し、症状発現時には早期に皮膚科受診を勧めるなどのきめ細かい指導も行っている。治療中の患者には日常生活において身体の変化に気を配ってもらい、外来受診日以外でも患者から症状を聞くことにより有害事象が悪化する前に早期に対応することが重要であると考えられた。

わが国における原発乳癌に対するFEC followed by docetaxel 100mg/m²併用療法による術前化学療法(FEC-DOC100)は、NSABP B-27と同様のpCRで高い効果が得られるレジメンであったが、実施に当たっては減量や有害事象に対する支持療法が必要であり、患者とのコミュニケーションを取りながら患者指導を行うことが重要であ