RESEARCH ARTICLE

Feasibility Study of Docetaxel and Cyclophosphamide Six-Cycle Therapy as Adjuvant Chemotherapy for Japanese Human Epidermal Growth Factor Receptor 2-Negative Breast Cancer Patients

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Abstract

Background: We compared treatment completion rates and safety of docetaxel and cyclophosphamide six-cycle therapy (TC6) with docetaxel followed by 5FU, epirubicin and cyclophosphamide (T-FEC) therapy in Japanese patients with human epidermal growth factor receptor 2 (HER2)-negative breast cancer. Materials and Methods: We administered TC6 q3w or T-FEC q3w to HER2-negative breast cancer patients. The primary endpoint of this trial was toxicity. As second endpoints, the treatment completion rate and relative dose intensity were evaluated. Results: The TC6 and T-FEC group consisted of 22 and 21 patients, respectively. Concerning hematological toxicity, grade 3 or higher adverse reactions included neutropenia and febrile neutropenia. As non-hematological adverse events, exanthema and peripheral neuropathy were frequently reported in the TC6 group, whereas more patients of the T-FEC group reported nausea and vomiting. In TC6, the treatment completion rate was 86.4% and the relative dose intensity of docetaxel was 93.2%. In T-FEC, the values were 95.2% and 98.9%, respectively. Conclusions: These results suggest that TC6 is tolerable in Japanese, and that this regimen can also be performed in outpatient clinics. However, with the TC6 regimen, the compliance was slightly lower than with the T-FEC regimen, and supportive therapy needs to be managed appropriately.

Keywords: Early breast cancer - adjuvant chemotherapy - cyclophosphamide - docetaxel - feasibility

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Introduction

The doxorubicin plus cyclophosphamide (AC) and cyclophosphamide, methotrexate and fluorouracil (CMF) regimens were used as the standard adjuvant chemotherapy regimens for breast cancer (Fisher et al., 2004; Bonadonna et al., 2005); taxane-based regimens were subsequently developed (Martin et al., 2005; Roche' et al., 2006). A meta-analysis of 13 randomized studies including 22,903 patients demonstrated that the addition of a taxane to an anthracycline-based regimen improved the disease-free survival (DFS) and overall survival (OS) of high-risk early breast cancer patients (De Laurentiis et al., 2008). Recently, there has been concern about cardiac toxicity caused by anthracycline drugs (Fumoleau et al., 2006), and so a non-anthracycline regimen was sought. Against this background, the US Oncology 9735 trial compared four cycles of docetaxel plus cyclophosphamide (TC) with four cycles of AC, and the TC group achieved significantly longer disease-free survival (DFS) and overall survival (OS) than the AC group (Jones et al., 2006). Since this trend was repeated in the subgroup analysis, TC was concluded to be the standard adjuvant chemotherapy for early breast cancer (Jones et al., 2009). This trial did not include a combined anthracycline-taxane regimen, however, and the US Oncology investigators have launched a new study (Clinical Trials.gov No. NCT00493870) in women with human epidermal growth factor receptor 2 (HER2)-negative tumors, comparing six cycles of adjuvant TC (TC6) with six cycles of docetaxel, doxorubicin and cyclophosphamide (TAC). However, there have been no reported studies that evaluated the feasibility of the TC6 regimen for early breast cancer patients. The aim of the present study was to investigate the feasibility of TC for six cycles and six cycles of sequential taxane and anthracycline regimen (T-FEC) in Japanese patients with HER2-negative early breast cancer, while using a six-cycle regimen.

Materials and Methods

Patient selection

Patients with HER2 negativity along with the following characteristics were eligible: histologically proven

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invasive breast cancer (female); T1-3, N0-2 or M0 Stage disease; aged between 20 and 65; an ECOG performance status of 0-1; prior lumpectomy or mastectomy; and normal end-organ and bone marrow function as defined by a leukocyte count of ≥3,500/JL, an absolute neutrophil count of ≥1,500/JL, a platelet count of ≥120,000/JL, a hemoglobin level of ≥10.0 g/dL, total bilirubin; AST; ALT; and alkaline phosphatase levels ≤ the upper limit of institutional normal (ULN), and a creatinine level ≤ the ULN. Eligible patients had normal cardiac function, as defined by a left ventricular ejection fraction (LVEF) of ≥50% on an echocardiogram and an ECG without evidence of uncontrolled arrhythmia. Patients were excluded for the following reasons: pre-existing ≥ grade 2 peripheral neuropathy; prior chemotherapy or hormone therapy as neoadjuvant or adjuvant therapy; a history of cancer or evidence of metastatic disease; being pregnant or nursing; allergies to polysorbate 80; or any uncontrolled or severe intercurrent illness including unstable angina, myocardial infarction within the past six months or severe infection. This study was conducted under the approval of the institutional review board of study center, and written informed consent was obtained from all patients.

Study design and treatment

The treatment schema is illustrated in Figure 1. This stratified randomization and parallel group adhered to good clinical practice (GCP) and the Declaration of Helsinki. The patients were randomized to two arms. The patients in the TC6 group received 75 mg/m^2 docetaxel by 60 min i.v. infusion and 600 mg/m^2 cyclophosphamide by 30 min i.v. infusion administered in an alternating manner every three weeks for six cycles, whereas the T-FEC group received 100 mg/m^2 docetaxel by 60 min i.v. infusion administered alternately every three weeks followed by 500 mg/m^2 fluorouracil by 30 min i.v. infusion, 100 mg/m^2 epirubicin by i.v. bolus and 500 mg/m^2 cyclophosphamide by 30 min i.v. infusion administered alternately every three weeks for three cycles. The patients were premedicated with antiemetic treatment involving a combination of 5-hydroxytryptamine-3 receptor antagonists and corticosteroids, sometimes in combination with antiemetic agents with a lower therapeutic index (dexamethasone 12 mg i.v. and granisetron 4 mg i.v. on day 1, and oral dexamethasone 8 mg on days 2-4 of DOC treatment; dexamethasone 20 mg i.v. and granisetron 4 mg i.v. onday 1, and oral dexamethasone 8 mg on days 2-6 with the FEC regimen). Granulocyte colony-stimulating factor (GCSF) could be used if the patient's neutrophil count fell to <500/lL or febrile neutropenia developed.

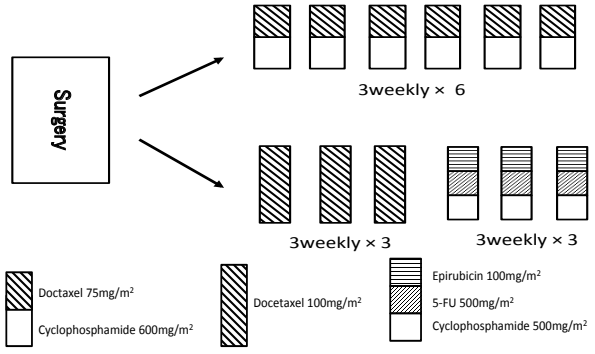

Figure 1. Schema of the trial

Dose reductions and delays

Toxicity was graded using the National Cancer Institute Common Toxicity Criteria for Adverse Events (CTCAE) version 3.0 throughout treatment with docetaxel, TC and FEC. The doses of docetaxel and FEC were reduced by 25% for febrile neutropenia or any grade 3 or higher non-hematologic toxicity (except nausea/vomiting or alopecia). In addition, the dose of docetaxel was reduced by 25% for grade 2 or higher peripheral neuropathy. Treatment could be postponed for up to two weeks if hematological or non-hematological toxicity had not resolved by the planned day 1 of the subsequent cycle. No dose re-escalation of the same drug in the same patient was allowed.

Statistical considerations

The primary endpoint of this trial was to determine the toxicity of TC6 compared with that of T-FEC. The incidence of grade 3/4 neutropenia for TC four-cycle regimen was 61% (Jones et al., 2006) and that for T-FEC regimens was 28.1% (Iwata et al., 2011). For the primary efficacy analysis, a sample of 21 patients in each group was required according to a binominal distribution, with a one-sided threshold of incidence of grade 3/4 neutropenia of 28%, an expected incidence of 38%, an α error of 5% and a β error of 10%. The secondary endpoint was to assess the number of patients in each group who completed all intended treatment cycles as well as the relative dose intensity (RDI). RDI per patient was calculated by dividing the total cumulative drug doses that the patient actually received per time (in mg/m^2/week). The mean RDI was then calculated for each treatment group. The distribution of patient characteristics between the two groups was compared using the chi square test. Descriptive comparisons were carried out using Fisher's two-sided exact test, without adjusting for multiple comparisons. The main analyses were conducted under the intention-to-treat principle.

Results

Patient characteristics

Forty-two patients were enrolled between August 2008 and May 2010 (Table 1). The median age of the subjects was 56 years (range, 39 to 65 years). All patients had an ECOG performance status of 0, 20% were premenopausal, 30% were estrogen receptor-positive, 53% were node-negative, 63% had Stage II disease, 23% were at pathological nuclear grade 1 and the mean number of positive axillary lymph nodes was 2.0 (range, 0-6). No characteristics differed significantly between the groups according to the chi square test.

Toxicity

A hematological survey was systematically performed in each group on day 8. Grade 3 or 4 leukopenia and neutropenia occurred frequently in both treatment groups (Table 2). Febrile neutropenia (FN) was observed in three

Table 1. Baseline Characteristics

		TC6 (n=22)	T-FEC (n=21)
Median age, yrs (range)		57 (40-65)	55 (39-62)
Stage	I	8	8
	IIA	12	10
	IIB	2	3
Nodal status	0	12	11
	1-3	10	9
	≤4	0	1
Nuclear Grade	1	5	5
	2	11	13
	3	6	3
Surgical procedure	Bp	5	17
	Bt	7	14
ER positive (%)		23	33

*TC6: six-cycle of docetaxel and cyclophosphamide; T-FEC: docetaxel followed by 5FU, epirubicin and cyclophosphamide

Table 2. Hematological Adverse Events (%)

	TC6 (Grade)		T-FEC (Grade)	
	1/2	3/4	1/2	3/4
Leucopenia	14	41	29	33
Neutropenia	9	41	29	33
Febrile neutropenia	0	14	0	0
Anemia	0	0	0	0
Thrombocytopenia	0	0	0	0

*TC6: six-cycle of docetaxel and cyclophosphamide; T-FEC: docetaxel followed by 5FU, epirubicin and cyclophosphamide

Table 3. Nonhematological Adverse Events (%)

	TC6 (Grade)		T-FEC (Grade)	
	1/2	3/4	1/2	3/4
Fatigue	41	5	38	14
Allergy	0	0	5	0
Nausea/Vomiting	9	0	33*	5
Decreased appetite	32	5	48	4
Stomatitis	18	0	33	0
Diarrhea	18	0	19	0
Rash/Eczema	23*	0	0	0
Neuropathy (sensory)	45**	5	10	4
Arthralgia	9	0	0	0
Myalgia	9	0	0	0
AST, ALT	9	0	10	0
Nail change	27	0	33	0
Peripheral edema	18	0	24	0

*p<0.05; **p<0.01); TC6: six-cycle of docetaxel and cyclophosphamide; T-FEC: docetaxel followed by 5FU, epirubicin and cyclophosphamide

patients (14%) in the TC6 group, but it was not observed in the T-FEC group. Percentages of treatment including GCSF were 27% in the TC6 group and 10% in the T-FEC group. The clinical safety of the two regimens differed with regard to their non-hematologic toxic effects (Table 3). More patients in the T-FEC group reported nausea and vomiting ($p<0.05$), whereas exanthema ($p<0.05$) and peripheral neuropathy ($p<0.01$) were frequently reported in the patients in the TC6 group. There were no patients exhibiting congestive heart failure.

Completion rate and dose intensity

The treatment regimens were generally well tolerated, but dose modifications and interval adjustments were necessary in 27% in the TC6 group and 24% in the T-FEC group. The completion rates were 86.4% in the TC6 group and 95.2% in the T-FEC group. There were three cases of treatment discontinuation in the TC6 group due to patient hopes and fatigue after four cycles of TC, and one case in the T-FEC group due to fatigue. The overall mean RDI for docetaxel were 93.2% in TC6 and 98.9% in T-FEC. There were no differences between the regimens with regard to RDI.

Discussion

In the treatment of breast cancer, recurrence of breast cancer will greatly affect the prognosis. Therefore, there is a need for a more optimal adjuvant regimen for breast cancer. Currently, it has been studied the therapeutic effect of TC6 cycles and TC4 cycles. In this study, we compared the safety and completion rate of TC6 in the Japanese, as a control group of FEC-DOC that has already been reported. This is the first reported study to evaluate the feasibility of the TC6 regimen for adjuvant chemotherapy in early breast cancer patients. The purpose of this trial was to compare the feasibility in patients treated with six cycles of the TC regimen and the T-FEC regimen. The main observed feature was the difference in toxicity profile between TC6 and T-FEC. In the NSABP-B-30 trial, 5,351 patients were randomly assigned to four cycles of docetaxel/doxorubicin/cyclophosphamide (TAC) or to four cycles of AC followed by four cycles of docetaxel versus four cycles of doxorubicin/docetaxel (AT); the trial found that AC followed by docetaxel was the superior regimen. In that trial, the results could have been related to the duration of therapy because they compared eight cycles of chemotherapy to four cycles of chemotherapy (Ganz et al., 2011). Eiermann et al. put the BCIRG 005 trial into the context of reported adjuvant chemotherapy studies; it was evident that both TAC for six cycles and AC for four cycles followed by docetaxel for four cycles were among the most active regimens currently available for the adjuvant treatment of HER2-nonamplified breast cancer (Eiermann et al., 2011). In the treatment of patients with lymph node-positive breast cancer, the question is whether six cycles of TC should be administered or whether four cycles of TC would be enough. To answer this question, the US Oncology group has embarked on a pivotal randomized phase III trial comparing six cycles of treatment with either TC or TAC in 2,000 HER2-negative patients (ClinicalTrials.gov No. NCT00493870).

In Japan, four cycles of TC therapy has become more common and its compliance was found to be tolerable (Takabatake et al., 2009). The PACS01 trial reported that sequential adjuvant chemotherapy with three cycles of fluorouracil, epirubicin and cyclophosphamide (FEC) followed by three cycles of docetaxel significantly improved DFS and OS (Roche' et al., 2006), and we reported previously that the T-FEC regimen might be more tolerable than FEC followed by docetaxel in Japanese breast cancer patients (Abe et al., 2012). There have been no reports about the feasibility of the TC6 regimen in HER2-negative breast cancer patients; therefore, we conducted this study to compare the toxicity and compliance rate between TC6 and T-FEC, while using

a six-cycle regimen. We expected fewer hematological adverse events and a higher compliance rate for the TC6 group than for the T-FEC group. The T-FEC regimen was associated with significantly more nausea and vomiting, but the TC6 regimen had more exanthema and peripheral neuropathy. The TC6 regimen was also associated with a somewhat higher rate of FN and slightly lower compliance than the T-FEC regimen. Neither prophylactic antibiotics nor GCSF were routinely used in this trial. The incidence of FN and the completion rate were 28.3% and 94.3% in TC four cycles in Japanese patients (Takabatake et al., 2009), and the incidence of FN and the completion rate in this study were 13.6% and 86.4%, respectively. There was no significant difference between these two reports. However, the completion rate at four cycles of TC6 was 100% in this study and we suggested that adverse events of the TC6 regimen would increase after four cycles.

In conclusion, TC six-cycle therapy is tolerable in Japanese patients and this regimen can also be performed at outpatient clinics. However, the compliance in the TC6 regimen was slightly lower than in the T-FEC regimen, so appropriate supportive therapy may be necessary, for which the use of prophylactic antibiotics should be considered for FN.

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