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Concurrent Administration of Trastuzumab and Anthracycline for Breast Cancer Treatment: An Unassailable Contraindication?

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Abstract

Anthracyclines have a severe adverse effect in cardiac function. Same here, trastuzumab has cardiotoxicity even in single use and also should lead to exacerbation of anthracycline-induced cardiotoxicity. Concurrent administration of anthracycline and trastuzumab is dangerous, but sequential administration is also dangerous. We should carefully design trastuzumab-containing regimens based on anthracycline dosing, regardless of whether it is concurrent or sequential. Contraindication of concurrent use of anthracyclines and trastuzumab has distracted us from its potential efficacy as well as from the inherent danger of anthracyclines together with trastuzumab. Avoidance of concurrent dosing is insufficient. As anthracyclines and trastuzumab are essential agents for HER2-positive breast cancer, and so, we must continue to address this issue from both safety and efficacy aspects.

Keywords: anthracycline, trastuzumab, cardiotoxicity, sequential or concurrent

1. Introduction: Cardiotoxicity and anthracyclines

Currently, anthracyclines, doxorubicin, and epirubicin remain as the representative key drugs for breast cancer treatment and are the most widely prescribed and effective cytotoxic drugs used in oncology. However, anthracyclines are well known to have severe adverse effects on cardiac function and to cause cardiomyopathy. Congestive heart failure (CHF) induced by anthracyclines depends on the cumulative administered dose and regimen schedule. The mechanism is thought to be direct myocardial injury due to the formation of free radicals and the prevalence of cardiomyopathy increases significantly when patients are given 550 mg/m²

of doxorubicin [1–3]. In particular, the estimated percentage of patients who develop CHF at a cumulative doxorubicin dose of 400 mg/m² is 3%, increasing to 7% at 550 mg/m² and to 18% at 700 mg/m². It was also reported that CHF is schedule dependent; the incidence was lower with a once-weekly schedule compared with a once tri-weekly schedule. In addition, the prevalence of CHF is increased in the young/elderly, after mediastinal XRT, females, and in those with a history of cardiac disease. Anthracyclines are still used in cancer therapy despite the existence of severe cardiotoxicity because it has irreplaceable anti-cancer effects. In most practitioner guidelines for breast cancer, anthracycline-including regimens are present, and this is also true for the National Comprehensive Cancer Network (NCCN) practitioner guidelines [4]. Due to the cumulative dose limitation and its difficult usage in cancer patients with worsening clinical conditions, we use anthracyclines only for preoperative or adjuvant therapy regimens and avoid using it for recurrent or Stage IV treatments. If we administer the “doxorubicin + cyclophosphamide (AC) cycled once per three-week regimen” according to the NCCN guidelines, doxorubicin is given at 60 mg/m² on day 1. Thus, the cumulative dose of doxorubicin would reach 360 mg/m² at 6 cycles. If we select the dose-dense regimen in which we administer AC once every 2 weeks, there may be altered cardiovascular risks, and the NCCN guidelines recommend it be stopped at 4 cycles. As described above, we must stop anthracycline regimens before 3 months even if excellent results are observed. Anthracyclines are fated to be administered for preoperative or adjuvant chemotherapy for radical cure, and after the administration of anthracycline-containing adjuvant therapy, they have no role in the treatment of recurrent cancer.

1. Anthracyclines have severe cardiotoxicity, and the prevalence of anthracycline-induced cardiomyopathy depends on the cumulative administered dose and regimen schedule.

2. Cardiotoxicity and trastuzumab

Trastuzumab is one of the most successful chemo-agents for molecular targeting therapy in breast cancer treatment. Amplification of the gene encoding the ErbB2 (Her2/neu) receptor tyrosine kinase and overexpression of Her2/neu protein are seen in approximately 20% of primary invasive breast cancers [5–7]. Trastuzumab (Herceptin®; Chugai Inc., Tokyo, Japan) is a humanized monoclonal antibody with high specificity for the extracellular domain of HER2/neu protein [8]. Single use of trastuzumab demonstrated modest antitumor activity, but in combination with standard chemo-agents (paclitaxel, docetaxel, doxorubicin, cyclophosphamide, and their combinations), trastuzumab exhibits synergic effects for cancer treatment. Indeed, combination protocols containing trastuzumab improved the time to progression, overall response, and duration of response and had a favorable impact on survival in several large-scale clinical trials [9–11].

In patients with metastatic breast cancer, the combination of trastuzumab with standard chemo-agents, anthracycline or taxanes resulted in longer times to progression (TTP), higher response rates, and higher survival rates than with those agents alone. Slamon et al. revealed that the combination of trastuzumab and AC provided the longest median time to disease progression (7.8 months) compared with other three arms— AC alone (6.1 months), paclitaxel

and trastuzumab (6.9 months), and paclitaxel alone (3 months) [12]. However, concurrent administration of AC and trastuzumab also lead to marked cardiotoxicity. The frequency of CHF was the highest in the concurrent AC and trastuzumab arm. The incidence of New York Heart Association class III or IV cardiac dysfunction was 16% in the concurrent AC and trastuzumab arm, whereas that in the AC alone arm was 3%, that in the paclitaxel and trastuzumab arm was 2%, and that in the paclitaxel alone arm was 1%. However, this result was predictable.

In order to administer AC regimens for 7.8 months (approximately 30 weeks), no less than 600 mg/m² of doxorubicin as a cumulative dose should be given, but 7–18% of patients will still develop CHF according to a report by Swain in 2001 [1, 3] even if concurrent trastuzumab is not administered. Slamon reported that less than 7% of the patients in the concurrent AC and trastuzumab arm exhibited chemo-induced cardiotoxicity associated with cumulative doses of doxorubicin of up to 550 mg/m². In his study, the cumulative dose of anthracycline was not identified as a compensated risk factor. Indeed, 16% as the prevalence of CHF in the concurrent AC + trastuzumab arm was not different from the expected percentage. Careful and regular checkup of cardiac function throughout the therapy, prompt intervention to abort administration if any complications occurred, and subsequent appropriate medical care for cardiac dysfunction likely led to this result.

In 2001, in addition to that by Slamon, one more important report was published. Cook-Bruns surveyed the safety data from 930 patients in trastuzumab-containing clinical trials and surveilled more than 25,000 patients who received trastuzumab in the USA [13]. She revealed that risk factors for cardiotoxicity are mainly related to prior or concomitant anthracycline exposure and that cardiotoxicity is unlikely to be induced by a single use of trastuzumab. Furthermore, she suggested a possible mechanism of cardiotoxicity due to anthracycline and trastuzumab use: anthracyclines directly damage the cardiomyocytes, and the following trastuzumab may interfere with growth and repair after anthracycline-induced damage.

Although HER2 receptor is not expressed in normal human cardiac myocytes, it was found to play an essential role in the developing embryonic heart [14–16]. Histological examination and echocardiography of hearts from adult ErbB2-conditional knockout mice demonstrated ventricular enlargement and increased left ventricle (LV) end-diastolic and end-systolic dimensions (LVEDD and LVESD), consistent with dilated cardiomyopathy [17]. HER2 signaling prevents cardiomyocytes from dilated cardiomyopathy and plays an important role in maintaining cardiac function in the adult heart.

Regardless of the study by Slamon, concurrent use of anthracycline and trastuzumab exhibits synergic anti-cancer effects as compared with concurrent use of paclitaxel. Thus, this regimen has potential, even if it should be limited to no more than 4–6 cycles and be performed with proper and regular monitoring by a physician. These conditions are acceptable for preoperative or adjuvant chemotherapy.

1. Anthracyclines induce cardiomyopathy, and the following trastuzumab may interfere with growth and repair of anthracycline-induced damage. From that perspective, concurrent use of trastuzumab with anthracycline and sequential use of trastuzumab following prior anthracycline have equal risks.

2. In preoperative or adjuvant chemotherapy with proper and regular monitoring of cardiac function, the number of cycles in a regimen can be artificially limited to avoid exceeding the applicable cumulative dose for anthracyclines.

From then on, however, the concurrent use of trastuzumab and anthracyclines has been regarded as a special protocol and is considered by most practitioners to be an “absolute” contraindication.

3. Concurrent use in adjuvant settings

As described above, concurrent administration of anthracycline and trastuzumab in adjuvant settings has the potential to revolutionize the treatment of breast cancer. However, to prevent irreversible cardiac damage, some conditions must be met, including a well-thought-out protocol, not administering anthracycline to its hazardous cumulative dose, and proper and regular monitoring of cardiac performance by specialists.

In 2005, Buzdar designed and implemented concrete strategies to examine this concept [18]. For preoperative chemotherapy, he designed a protocol of concurrent anthracycline (epirubicin) and trastuzumab and demonstrated its excellent efficacy and safety for HER2-positive breast cancer. In this trial, significant pCR rates favoring the trastuzumab plus chemotherapy arm were noted before reaching the planned full sample size, and new recruitment was therefore suspended by their Data Monitoring Committee. Indeed, a marked difference in the two arms was observed in this trial; 26.3% of patients in the chemotherapy alone arm achieved pCR as compared with 65.2% of the patients treated with trastuzumab plus chemotherapy. The cardiac function of enrolled patients was strictly monitored, and repeated evaluation was performed at baseline and after the completion of each regimen. Patients older than 75 or with a history of uncompensated congestive heart failure or a cardiac ejection fraction less than 45% were excluded. As a result, no patients developed drug-induced congestive heart failure.

In our opinion, this spotless outcome of this trial was due to the following:

1. Buzdar started the protocol with weekly paclitaxel + trastuzumab prior to concurrent epirubicin (as FEC75, q3w 75 mg/m² Day 1) + trastuzumab in this trial. This order, taxanes followed by anthracycline, was different from protocols by other practitioners at the time.

In 2003, Bear HD reported the results of the NSABP-B27 trial [19]. He administered four cycles of preoperative AC, which was the standard chemotherapy at the time, followed by adding four cycles of docetaxel. The NSABP-B27 trial demonstrated the efficacy of adding docetaxel regarding pathological response rates and overall survival of patients with operable breast cancer. In addition, two large prospective trials (NSABP B-28 and CALGB 9344) were performed to assess the efficacy of paclitaxel given sequentially after anthracycline-based chemotherapy [20, 21]. At that time, the effects of adding taxanes were unclear, and they were therefore commonly added after AC.

Why did Buzdar select the uncommon sequence?

In the regimen of AC followed taxanes, AC is administered at the beginning of chemotherapy. In tri-weekly regimens, doses for 3 weeks should be administered at once at the start of chemotherapy. In Buzdar's protocol, the weekly dose of paclitaxel, which has less cardiotoxicity than doxorubicin, was initially administered with the concurrent trastuzumab. Based on data from us and Buzdar, marked downregulation of LVEF due to trastuzumab is likely if paclitaxel + trastuzumab are initially administered [22, 23]. Therefore, the period at the start of paclitaxel + trastuzumab may be used to screen for possible trastuzumab-induced cardiotoxicity. Patients with cardiac dysfunction or cardiomyocyte disorders will be revealed in this paclitaxel + trastuzumab phase. Practitioners must not overlook signs and symptoms during regular monitoring in order to safely proceed to the next anthracycline + trastuzumab phase.

2. Buzdar selected epirubicin instead of doxorubicin, and he administered the low dose of 75 mg/m^2 rather than 100 mg/m^2 . As described above, the risk of CHF is highly correlated with the cumulative anthracycline dose. In breast cancer treatment, there are two representative anthracyclines: doxorubicin and epirubicin. At equivalent doses, they both have the same efficacy, but epirubicin has a better cardiac safety profile. Indeed, the doxorubicin-to-epirubicin dose ratio that produces a similar degree of cardiac toxicity is 1:1.8 [24]. The French Adjuvant Study Group (FASG) previously investigated the influence of dose escalation of epirubicin by comparing fluorouracil at 500 mg/m^2 , epirubicin at 50 mg/m^2 , and cyclophosphamide at 500 mg/m^2 every 21 days for six cycles (FEC 50) with the same regimen except with epirubicin at 100 mg/m^2 (FEC100). After 5 years of follow-up, FEC100 significantly improved the DFS and OS, and the risk of cardiotoxicity by the dose escalation in FEC100 was acceptable [25], even after more than 8 years of follow-up [26]. However, as dose escalation to FEC100 was unconventional at that time, FEC75 was paired with trastuzumab in many anthracycline-containing regimens.
3. This research was performed in preoperative setting; therefore, there should be 1- to 2-month break between the end of FEC75 + trastuzumab and the following 6-month trastuzumab for breast surgery and radiotherapy. Based on Cook-Bruns hypothesis that anthracyclines induce cardiomyopathy and trastuzumab may interfere with growth and repair, this interval should give the damaged cardiomyocytes time to recover. However, it remains unclear whether a 2-month break was sufficient for the cardiomyocytes to return to their former state.

4. Description in the NCCN guidelines about the concurrent use of anthracycline and trastuzumab

Following the disclosure of Buzdar's results, the regimen of weekly paclitaxel with concurrent trastuzumab, followed by FEC75 with concurrent trastuzumab, was described in the NCCN practitioner guidelines as their recommendation for preoperative chemotherapy. However, they also stated that the concurrent use of anthracycline and trastuzumab is a contraindication due to the risk of cardiotoxicity, and thus Buzdar's regimen was treated as an exception. The regimen is in the NCCN guidelines published in 2009 (http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf) [27], and the additional comment is written on the same page:

“Trastuzumab should not be given concurrently with an anthracycline because of cardiotoxicity, except as part of the neoadjuvant trastuzumab with paclitaxel followed by CEF regimen.”

This was likely an incentive for Buzdar to establish the cardiac safety of his concurrent regimen to confirm that the concurrent administration improved outcomes, was more precise, and improved the pCR rate in preoperative chemotherapy compared with sequential administration. The American College of Surgeons Oncology Group (ACOSOG) Z1041 trial was carried out, and patients with HER2-positive breast cancer were randomly assigned to the sequential regimen, FEC75 followed by paclitaxel + trastuzumab, or the concurrent regimen, paclitaxel + trastuzumab followed by FEC-75 + trastuzumab [28], and compared. The study results were published in 2013, and marked asymptomatic decreases in the left ventricular ejection fraction (LVEF) during chemotherapy were noted in similar proportions of patients in each group. However, no improvement in pCR rate was observed in the concurrent treatment group compared with the sequential group. Thus, if there is no difference between the performance of concurrent and sequential regimens, concurrent regimens can be avoided. Following the Z1041 trial, the concurrent regimen of anthracyclines and trastuzumab was removed from the NCCN guidelines, and only the statement about contraindication remains.

However, some questions remain unanswered. As a prerequisite for treatment in preoperative and adjuvant settings, sequential delivery of anthracyclines and trastuzumab has not been confirmed as safer than concurrent use. Dang [29] investigated the safety of dose-dense AC followed by paclitaxel + trastuzumab and demonstrated cardiac safety because only one patient (1%) developed CHF and 7% of the patients exhibited asymptomatic LVEF decline during the administration. On the other hand, in the Z1041 trial, LVEF fell below the institutional lower limit of normal for six patients (4–6%) in the concurrent group. The patients in the Z1041 trial did not develop CHF. As a result of this phase II study on 70 patients, the cardiac outcome was not poor, but no better than that for the 142 patients in the concurrent arm in the Z1041 trial. This regimen, dd-AC followed by weekly paclitaxel + trastuzumab, is included in the recommendation by the latest NCCN guidelines for preoperative chemotherapy.

Next, if the initial administration of weekly paclitaxel + trastuzumab can be used to detect potential trastuzumab-induced cardiotoxicity, the dd-AC regimen should be postponed until the weekly paclitaxel + trastuzumab regimen is finished without any cardiac incidents.

In addition, the replacement of the dd-AC regimen with dd-EC regimen or FEC100 regimens is unclear. Concurrent administration of anthracycline and trastuzumab is dangerous, but sequential administration is also dangerous. We should carefully design trastuzumab-containing regimens based on anthracycline dosing, regardless of whether it is concurrent or sequential. The potential risk of trastuzumab-induced cardiotoxicity is not nullified by simply avoiding concurrent use with anthracyclines.

5. Entrance of pertuzumab: TRYPHAENA, NeoSphere, and APHINITY

There has been a recent innovation in anti-HER2 therapy. The new agent “pertuzumab” is a humanized monoclonal antibody that binds HER2 at a different epitope of the HER2

extracellular domain than where trastuzumab binds [30]. This new molecular-targeted agent prevents HER2 from dimerizing with HER3 [31], and trastuzumab and pertuzumab, when given together, exhibit synergic effects to block HER2 signaling, resulting in greater antitumor activity than either agent alone [32]. In the treatment of metastatic breast cancer, the CLEOPATRA trial successfully demonstrated that the combination of pertuzumab + trastuzumab + docetaxel, as compared with the standard docetaxel-trastuzumab regimen, significantly improved progression-free survival, without escalating cardiac toxicity [33, 34].

In the preoperative setting, TRYPHAENA [35, 36] and NeoSphere [37] also nearly doubled the pCR rate, as observed by the synergic effects of trastuzumab and pertuzumab. In July 2017, the APHINITY trial revealed that the addition of pertuzumab to trastuzumab-containing conventional chemotherapy improved invasive disease-free survival as adjuvant treatment [38].

The protocols of these pertuzumab-containing trials were designed before the disclosure of the Z1041 trial; therefore, the patients in the TRYPHAENA trial were given pertuzumab and trastuzumab simultaneously with FEC100 (5-fluorouracil: 500 mg/m²; epirubicin: 100 mg/m²; cyclophosphamide: 600 mg/m²) (**Figure 1**). Of note, the concurrent administration of anthracycline and anti-HER2 agents was performed before the taxane-containing regimen. However, this protocol has a prerequisite cumulative dose of anthracycline (as Epirubicin, 300 mg/m²; 300 mg/m² in the Z1041 protocol), and the patients should have drug holidays after the concurrent administration.

Regarding the efficacy of these protocols, the preoperative pCR rates in the TRYPHAENA trial were 61.6% (ypT0/is) and 50.7% (ypT0/ypN0), and it was 45.8% in the NeoSphere trial. Compared with the concurrent dosing arm in the Z1041 trial (pCR rate was 54.2%), these outcomes were not improved. This is likely because both TRYPHAENA and NeoSphere trials administered the sequential taxane or anthracycline postoperatively, whereas it was given preoperatively in the Z1041 trial. Cardiac safety was maintained in all trials and no patients developed CHF.

The next question is whether the addition of pertuzumab to the Z1041 regimen will escalate the pCR rate in the preoperative setting. If yes, it should surpass the outcomes by TRYPHAENA and NeoSphere. In practice, trastuzumab was given every 3 weeks at 8 mg/kg, followed by 6 mg/kg from its initiation. The pertuzumab loading dose was 840 mg, followed by 420 mg every 3 weeks. Docetaxel was given at 75 mg/m² every 3 weeks. After completion of four cycles, eligible patients underwent the next regimen. The following FEC75 therapy (four cycles of fluorouracil at 500 mg/m² intravenously, epirubicin at 75 mg/m² intravenously, and cyclophosphamide at 500 mg/m² intravenously every 3 weeks) was administered with concomitant trastuzumab at 2 mg/kg on days 1, 8, and 15 of the 21-day cycle for four cycles (**Figure 1**). Then, the patients underwent surgery, radiotherapy, and standard hormone treatment for ER-positive patients according to the guidelines. After surgery, and if needed, after radiotherapy, patients should continue trastuzumab for a total duration of 1 year from the start of neoadjuvant therapy.

This regimen, T(rastuzumab)-P(ertuzumab)-D(ocetaxel) followed by FEC75 - T(rastuzumab) has not yet been evaluated in a phase II trial, but its efficacy and feasibility should be predictable as an extension of the previous studies described above. The cardiac feasibility of each regimen, T-P-D and FEC75-T, was established using either regimen alone but was insufficient in combination. However, the anti-cancer performance of this regimen is promising.

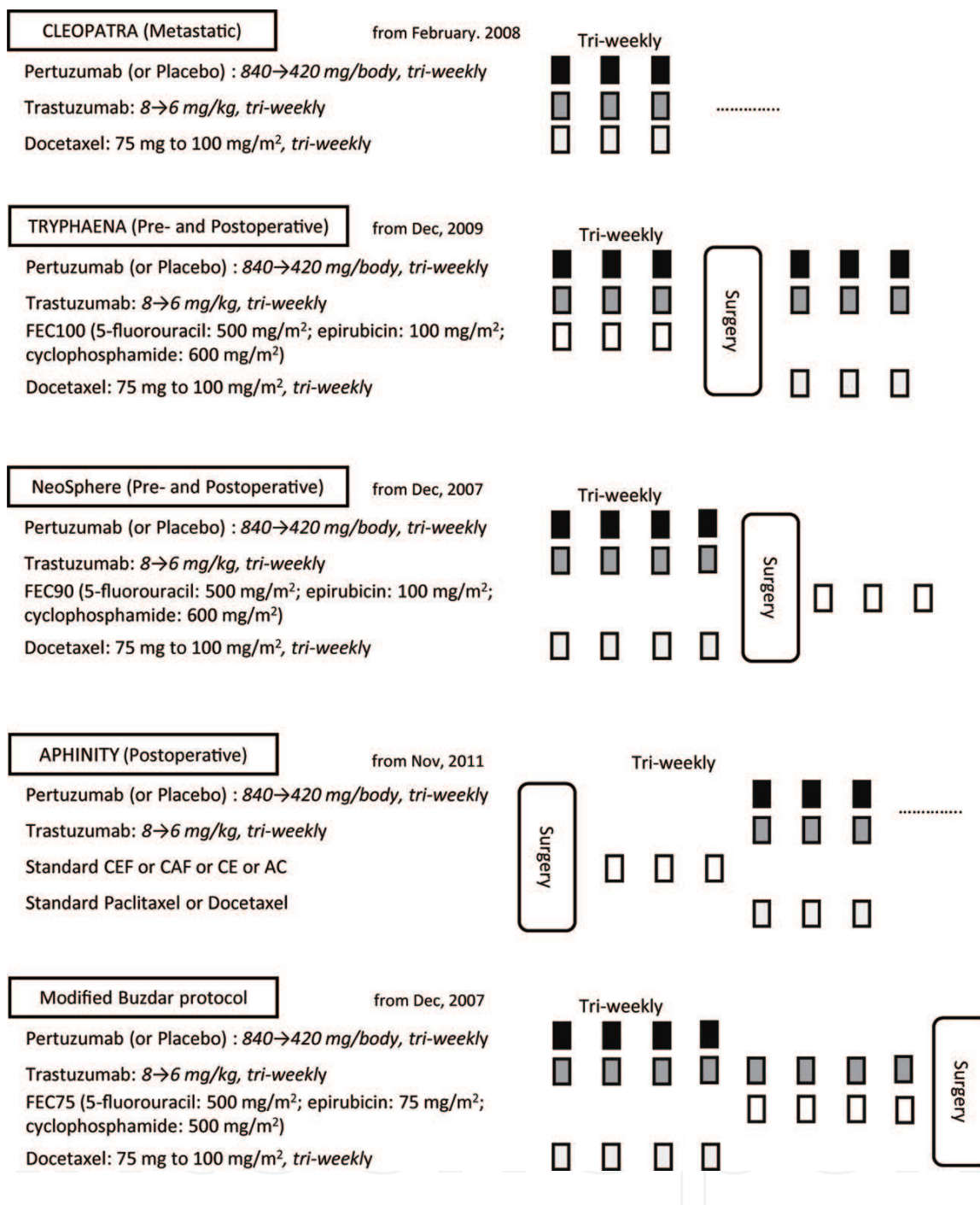


Figure 1. Schema of each protocols, given in this manuscript.

6. Neoadjuvant chemotherapy; Trastuzumab-Pertuzumab- Docetaxel followed by FEC75-Trastuzumab

6.1. Patients and protocol

Following the CLEOPATRA (2010) trial and when the Japanese public insurance began covering pertuzumab (August 2013), we adopted pertuzumab at our hospital and have performed

the T-P-D regimen as the standard chemotherapy for HER2-positive metastatic breast cancer. Prior to this, we performed the Buzdar regimen, weekly paclitaxel + trastuzumab, followed by concurrent FEC75 + trastuzumab, as the standard preoperative chemotherapy for HER2-positive breast cancer. Therefore, since the disclosure of TRYPHAENA (2013) and NeoSphere (2012) trials, we shifted to the following regimen: T-P-D followed by FEC75-T, as the pre-operative chemotherapy for patients with advanced breast cancer. After approval from our institutional review board, we have administered this regimen to 24 patients at our hospital between October 2015 and May 2018, and we finished the protocol in 23 (**Table 1**). Except the one recent patient with T1 N0 Stage I cancer, all patients had advanced breast cancer and three had distant metastasis.

The administration of T-P-D was established by the CLEOPATRA trial, and FEC75-T was also established and familiar to us. Thus, we did not design the phase II trial for this protocol, which is why we did not administer pertuzumab concurrently with FEC-T.

Total (n)	24
Age, average \pm STD (min. – max.)	54.3 \pm 1.0 (32–70)
Body-mass index, average \pm STD (min. – max.)	22.2 \pm 4.1 (17.33–36.68)
Taking drugs for diabetes (+/–)	1/23
Taking drugs for hypertension (+/–)	1/23
Histology	Invasive ductal carcinoma, 23 Mucinous carcinoma, 1
ER –, PgR – (n)	10
ER +, PgR –	5
ER –, PgR +	0
ER +, PgR +	9
Baseline LVEF (%) [§]	61.7 \pm 3.2 (55.0–67.5)
Baseline LVDd (mm)	44.8 \pm 5.9 (27.1–57.6)
Clinical stage I/II/III/IV (total) (n)	1/12/7/3 (23)
Clinical T 1/2/3/4 (total)	1/12/4/6 (23)
Clinical N 0/1/2/3 (total) [¶]	9/11/2/1 (23)
Clinical M 0/1 (total) [¶]	20/ 3 (23)
Disease free survival (months) [¶]	9.6 \pm 5.8 (0–22.4)

[§]Left ventricular ejection fraction was measured by echocardiography at primary therapy, completion of each regimen, and after 1 year from the completion of chemotherapy.

[¶]No recurrence of cancer was noted in these 24 patients, and disease-free survival was thus equal to the follow-up period. Three patients had distant metastasis: Case 1 with liver metastasis, Case 2 with bone metastasis, and Case 3 with bone, pulmonary, and mediastinal lymph node metastasis. These metastases have remained at clinical complete response or not progressed.

[¶]We routinely performed positron emission tomography (PET) with 18F-fluorodeoxyglucose (FDG) in the patients to access lymph node involvement or distant metastasis at baseline.

Table 1. Characteristics.

All patients underwent an initial cardiac-echogram evaluation, including left ventricular ejection fraction (LVEF) measurements. Patients with a history of congestive heart failure or a cardiac ejection fraction less than 50% were excluded.

Histological confirmation of the invasive tumor was performed on the specimen taken by core needle biopsy or ultrasound-guided vacuum-assisted breast biopsy. The biopsy samples were also examined for HER2 overexpression by fluorescence in situ hybridization (FISH) or 3+ overexpression by immunohistochemistry (IHC) and for estrogen and/or progesterone receptor expression.

Before initiation of therapy, all patients underwent staging evaluation, which included a complete history, physical examination, CBC, chemistry profile, chest radiography, and 18F-fluorodeoxyglucose positron emission tomography (FDG-PET). Tumor size and extension were examined by contrast-enhanced magnetic resonance imaging (MRI-CE). The imaging studies of the tumors were routinely performed at initiation, after T-P-D, and after FEC-T. Tumor shrinkage (objective response) and disease progression were assessed using the RECIST guidelines (version 1.1) [39].

On each hospital visit, we routinely checked the subjective cardiac symptoms and associated objective findings. Cardiac echocardiogram was routinely obtained at baseline, after T-P-D, after FEC-T, and additionally at 12 months after surgery. All echoes were two-dimensional and transthoracic. If abnormal data were obtained, all were interpreted by cardiologists at our hospital. We defined decreased LVEF as an absolute 10-point decrease in LVEF from baseline or an LVEF of 50%.

6.2. Response to chemotherapy

Only 20.8% of patients achieved complete clinical response (cCR) after P-T-D and the rate increased to 54.2% after FEC75-T. Of note, 37.5% of tumors maintained their objective size (stable disease) even after FEC75-T on contrast-enhanced MRI (**Table 2**).

Figure 2 shows the objective responses for each patient throughout preoperative chemotherapy. After the P-T-D regimen, only five patients achieved cCR, but by the addition of FEC75-T, 13 achieved cCR.

Pathological complete response (pCR; Grade 3) was noted in 73.9% of patients, and by adding Grade 2b, the excellent response rate reached 82.6%. Although there were two patients with Grade 0 response, they initially had large tumors (42.7 mm (mucinous carcinoma) and 124.1 mm (solid-tubular carcinoma)).

6.3. Ejection fraction

No incidence of congestive heart failure has been observed, but two patients had an absolute 10-point decrease from the baseline LVEF, one of whom declined in the FEC75-T phase (**Figure 3**). However, all patients maintained EF over 50% throughout chemotherapy, and no patients stopped chemotherapy due to cardiac adverse events. Including the three patients with distant metastasis, we performed surgery on all patients to achieve local control, to

Phase	P-T-D	FEC75-T
Clinical (n = 24) response*		
CR	5 (20.8%)	13 (54.2%)
PR	14 (58.3%)	2 (8.3%)
SD	5 (20.8%)	9 (37.5%)
PD	0	0
Pathological (n = 23) response [†]		
Grade 3 [‡]		17 (73.9%)
Grade 2 (Grade 2a, n = 2; Grade2b, n = 2)		4 (17.4%)
Grade 1		
Grade 0 [§]		2 (8.7%)

P-T-D: Trastuzumab was given every week at 4 mg/kg followed by at 2 mg/kg from its initiation. The pertuzumab loading dose was 840 mg, followed by 420 mg every 3 weeks. Docetaxel was given at 75 mg/m² every 3 weeks. Pertuzumab and docetaxel were administered for four cycles.

FEC75-T: FEC75 therapy (four cycles of fluorouracil at 500 mg/m² intravenously, epirubicin at 75 mg/m² intravenously, and cyclophosphamide at 500 mg/m² intravenously every 3 weeks) was administered with concomitant trastuzumab at 2 mg/kg on days 1, 8, and 15 of the 21-day cycle for four cycles.

We always started our protocol with P-T-D, followed by FEC75-T.*Clinical and pathological response of the tumor was judged according to the RECIST guidelines.

[†]Pathological examination was performed after surgery on the surgical specimen.

[‡]Grade 3, n = 8; Grade 3 + 3(n,) n = 3; Grade 3 + 3(n) + 3(d), n = 6.

[§]These two patients had comparably large tumors and their initial sizes were 42.7 mm (mucinous carcinoma) and 124.1 mm (solid-tubular carcinoma), respectively, on MRI-CE. Both patients had lymph node metastasis, but the final pathological examination revealed excellent efficacy for metastasis (Grade 0 + 3(n)).

Table 2. Tumor response to neoadjuvant chemotherapy.

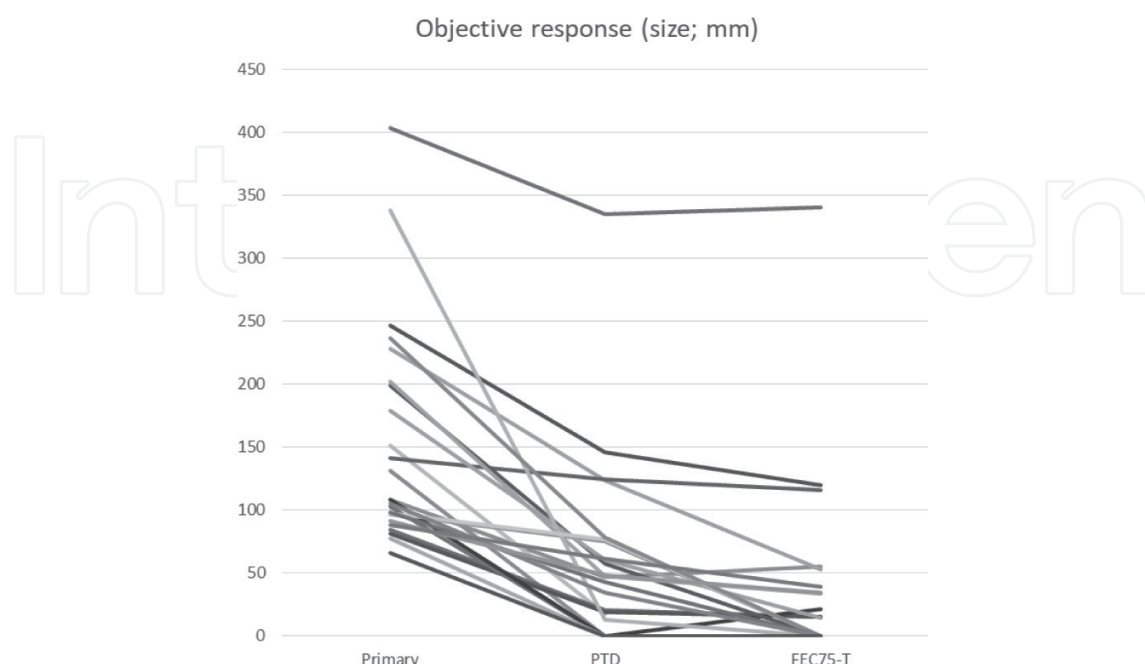


Figure 2. Objective response accessed by contrast-enhanced MRI.

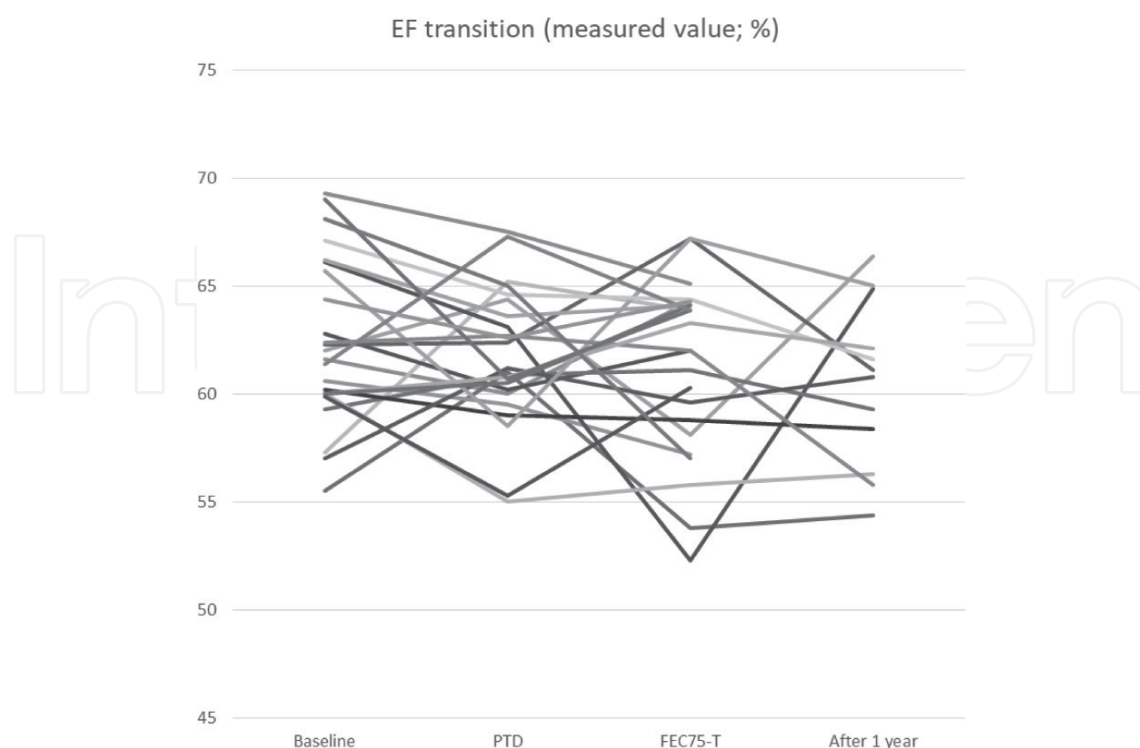


Figure 3. Transition of ejection fraction (EF).

manage discharge, to maintain activities of daily living, and as a surrogate measurement of the response of metastasis.

We have already followed and accessed the EF data of 12 patients for 1 year after the surgery, and no severe adverse events were observed.

6.4. Comprehensive analysis of adverse events

Other frequent complication data are listed in **Table 3**. The patients tolerated the regimen well. We administered pegfilgrastim (recombinant human granulocyte colony-stimulating factor analog filgrastim) to four patients due to febrile neutropenia. The onset of febrile neutropenia occurred in the P-T-D phase and pegfilgrastim was continued until the end of preoperative therapy.

7. Lessons learned from evaluations

Based on our experience, this concurrent regimen: T(rastuzumab)-P(ertuzumab)-D(ocetaxel) followed by FEC75 - T(rastuzumab) may be feasible and powerful, although our sample size was too small to compare with other pertuzumab-containing trials such as TRYPHAENA and NeoSphere. However, as concurrent administration of anthracyclines and trastuzumab is currently contraindicated, the synergic effects of these drugs are unable to be evaluated. Our regimen and its outcome should challenge this current stance.

	Grade 1	Grade 2	Grade 3	Grade 4
Hematological				
Anemia	4 (17.4%)	8 (34.8%)	0	0
Leukocytopenia	2 (8.7%)	5 (21.7%)	6 (26.1%)	0
Neutropenia	2 (8.7%)	3 (13.0%)	5 (21.7%)	3 (13.0%)
Non-hematological, non-cardiac				
Nausea	14 (60.9%)	3 (13.0%)	1 (4.3%)	0
Constipation	8 (34.8%)	2 (8.7%)	0	0
Diarrhea	9 (39.1%)	3 (13.0%)	0	0
Fatigue	16 (69.6%)	3 (13.0%)	0	0
Stomatitis	11 (47.8%)	3 (13.0%)	0	0
Neurosensory disorder	12 (52.2%)	2 (8.7%)	0	0
Cardiac				
Congenital heart failure	0	0	0	0
LVEF measurement				
<10% decrease from baseline, above LLN	12 (52.2%)			
>=10% decrease from baseline, above LLN	2 (8.7%)			
below LLN	0			

LLN = lower limit of institutional normal; 50%.

Table 3. Comprehensive analysis of adverse events.

Buzdar reported in the Z1041 trial that 54.2% of patients in the concurrent group of weekly paclitaxel with trastuzumab followed by FEC75-T had a pathological complete response ($n = 142$, 45.7–62.6) [28]. In the concurrent group in TRYPHAENA, FEC + T + Pertuzumab → Paclitaxel + T + pertuzumab, 61.6% had a pathological complete response ($n = 72$) [35], and in NeoSphere, 45.8% in the sequential group of P-T-D had a pathological complete response ($n = 107$, 36.1–55.7) [37].

In the concurrent arm in the Z1041 trial, one patient developed Grade 4 cardiac ischemia and Grade 3 left ventricular systolic dysfunction (0.7%), and in TRYPHAENA, symptomatic left ventricular systolic dysfunction (grade ≥ 3 , severe adverse event) was noted only in the sequential arm, FEC → Paclitaxel + T + pertuzumab. Although there was no arm for concurrent administration in NeoSphere, one patient in the pertuzumab and trastuzumab arm developed CHF.

Concurrent administration of anthracyclines and trastuzumab can be dangerous, and this was confirmed in the treatment of metastatic carcinoma with indiscriminate continuous dosing. However, sequential dosing is also dangerous. Indeed, it remains unclear whether their synergic toxicity is attributable to their concurrent use and whether we can avoid the cardiac events as long as we use them sequentially. In previous studies on anti-HER2 agents

for preoperative and adjuvant chemotherapy, distinctive characteristic cardiotoxicity was not observed in the concurrent arms.

As described by Cook-Bruns, patients who have received prior anthracyclines are at higher risk for cardiotoxicity even with trastuzumab monotherapy. Prior anthracycline dosing may be the cause of trastuzumab-related heart failure. As trastuzumab and anthracycline are essential agents for HER2-rich breast cancer, we must continue to address this issue from both safety and efficacy aspects. In the TRYPHAENA and NeoSphere trials, detailed monitoring was needed to prevent cardiac adverse events. However, the protocol combining preoperative and postoperative chemotherapy to take drug holidays was complicated for practitioners and patients. The patients undergoing these sequential protocols need an additional 3 months of trastuzumab and hospital visits compared with the concurrent regimen. Moreover, the correlation between the effects of preoperative treatments on pCR and treatment efficacy for survival outcomes becomes unclear.

Contraindication of concurrent use of anthracyclines and trastuzumab has distracted us from its potential efficacy as well as from the inherent danger of anthracyclines together with trastuzumab. Avoidance of concurrent dosing is insufficient. For practitioners, upholding the upper limit of the cumulative dose for anthracyclines, taking every available survey to exclude high-risk candidates, checking and following the patients' cardiac function carefully, and never overlooking the signs of asymptomatic cardiac dysfunction are of the utmost importance.

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