Capecitabine + Epirubicin + Cyclophosphamide Combination Therapy (CEX Therapy) as Neoadjuvant Chemotherapy for HER-2-Negative Breast Cancer: A Retrospective, Single-Center Study

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Background: We modified and administered capecitabine + epirubicin + cyclophosphamide combination therapy (CEX) as neoadjuvant chemotherapy (NAC) for HER-2-negative breast cancer and retrospectively analyzed its effectiveness and tolerability at our center.

Methods: The inclusion criteria were presence of breast cancer negative for HER-2 and positive lymph node metastasis, or negative lymph node metastasis when tumor diameter was 20 mm or greater without distant metastasis. Additional inclusion criteria were a performance status of 0 or 1, an EF >60%, and an age of 75 years or less. Clinical outcomes were evaluated after 4 courses of epirubicin 80 mg/m², cyclophosphamide 500 mg/m² (administered every 3 weeks), and capecitabine 1,500 mg/m² (administered for 2 weeks and withdrawn for 1 week).

Results: A clinical benefit was noted in all 18 patients who received CEX as neoadjuvant chemotherapy during the period from 2009 through 2013. The clinical response rate was 83.3% (15/18), and the clinical complete response rate was 50%. Aesthetic outcomes of breast-conserving surgery were positive in all patients. Among patients with satisfactory outcomes, 33.3% had a pathologic complete response (triple-negative: 6, luminal: 0) and 68.8% were n0 (triple-negative: 8, luminal: 3). All patients with a pathologic complete response are presently alive, free of recurrence, and currently undergoing follow-up. Adverse events were classified as grade 2 or lower in all patients.

Conclusions: CEX therapy administered as neoadjuvant chemotherapy could be useful for individualized treatment. In particular, this regimen was effective for triple-negative breast cancer.

Key words: breast cancer, neoadjuvant chemotherapy, ‘CEX’, triple-negative, pathologic complete response

Introduction
Recently, detailed studies of histopathologic features—including intrinsic subtypes, expectations for combining ideal evidence, and personalized treatment approaches—have been increasing in breast cancer treatment. In particular, a high pathologic complete response (pCR) rate was reported for patients with HER-2-type cancer treated with chemotherapy regimens including trastuzumab as a key drug, including those with recurrent progressive metastatic breast cancer and those receiving adjuvant therapy (AT) or neoadjuvant chemotherapy (NAC). In HER-2-negative breast cancer, namely, luminal or triple-negative (TN) cancer, a regimen of 5-fluorouracil (5-FU) + epirubicin + cyclophosphamide (FEC), followed by tax-
ane, is frequently considered and is widely recognized in Japan as an NAC regimen\textsuperscript{11-15}. However, the outcomes of this treatment are unclear\textsuperscript{16,17,19}. The pCR rate was 20% to 30%; thus, some targeted patients who experienced high-grade adverse events for nearly 6 months might be discouraged from receiving further treatment or restarting treatment after recurrence. Therefore, an NAC regimen should be established for this type of breast cancer, particularly one with a high response rate and good tolerability, assuming preoperative AT would be performed\textsuperscript{20,22}.

One such potential regimen is capecitabine + epirubicin + cyclophosphamide combination (CEX) therapy, which replaces the 5-FU in FEC with capecitabine, an oral pyrimidine fluoride drug\textsuperscript{23-28}.

In 2009, we have modified and began administering CEX therapy as a NAC regimen for HER-2-negative breast cancer without distant metastasis. This retrospective study investigated the effectiveness and tolerability of this therapy at our center.

Materials and Methods

Patients and Eligibility Criteria

We collected and analyzed data from all patients with histologic evidence of HER-2-negative invasive breast cancer, with lymph node metastasis or (in patients with primary breast cancer negative for lymph node metastasis) a tumor diameter of 20 mm or larger without distant metastasis. Additional inclusion criteria were age younger than 75 years, absence of other tumors at the start of treatment, and no history of preoperative cancer treatment; a white blood cell count >3,000/μl (neutrophil count >1,000), hemoglobin >10.0, Plt >100,000, EF >60% for cardiac functions, and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. All patients were adequately informed of this clinical trial and submitted written informed consent.

Patients were excluded if (1) the data were incomplete for reasons such as transfer to another center, (2) consent was withdrawn, (3) they did not satisfy all eligibility criteria, (4) they had social or economic restrictions, and (5) they were otherwise unable to continue treatment.

The primary endpoint was pCR rate, and the secondary endpoints were (1) rate of breast-conserving surgery, (2) clinical response rate, and (3) safety (severity of adverse events). Anti-tumor evaluation was made by using the RECIST criteria and was classified as complete response (CR), partial response (PR), stable disease (SD), and progressive disease and clinicopathologically as clinical CR (cCR) and pathologic CR (pCR).

The administered drugs are approved in Japan and other countries and are commonly used clinically. Evaluation of adverse events and countermeasures can be done in daily practice. Adverse events were evaluated by using the Common Terminology Criteria for Adverse Events (CTCAE) ver. 4.0.

As in previous studies, treatment was discontinued or changed when disease progressed and no response was seen, when patients developed Grade 4 adverse events, or when patients declined or requested discontinuation of treatment. This study was conducted in accordance with the principles of the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of Nippon Medical School Tama Nagayama Hospital (approval number, 591).

Details of the Regimen (CEX-NAC)

Clinical evaluations—including CT, ultrasonography (US), and MRI—were made after completion of 4 courses of epirubicin 80 mg/m$^2$ + cyclophosphamide 500 mg/m$^2$ (both administered every 3 weeks) and capecitabine 1,500 mg/m$^2$ (administered for 2 weeks and withdrawn for 1 week). We used lower than usual dosing to achieve both a high response rate and high tolerability. If Grade 3 hematologic adverse events developed, we planned to reduce the dose of chemotherapeutic agents to 85% of the initial dose and change the interval of chemotherapy administration (postponed by 1 week). On the basis of previous results, we expected a clinical response rate (CRR) of 70% and a pCR rate of 20%.

Results

Eighteen patients were eligible to receive CEX-NAC during the period from 2009 through 2013, and all completed treatment: 7 had luminal breast cancer and 11 had TN breast cancer. A clinical benefit was noted in all patients (CR + PR + SD): the RR (CR+PR) was 83.3% (15/18) and the cCR was 50% (TN: 6, luminal: 3). Breast-conserving surgery (Bp) yielded positive aesthetic outcomes in all patients, and axillary lymph node dissection (Ax) was performed for 16 patients with lymph node metastasis; sentinel node biopsy was performed for only 2 node-negative patients. Histopathologic results were also satisfactory: the pCR rate was 33.3% (6/18; TN: 6, luminal: 0), and 68.8% (11/16) had no cancer (TN: 8, luminal: 3) (Table 1). The clinical findings of patients treated with CEX-NAC are shown in Figures 1~3.

Among patients who did not achieve pCR, adjuvant chemotherapy with taxane agents was performed for
Table 1 Patients and results of CEX-NAC

| No. | Age | area | T | N | H. | sub-type | Clinical status | Surgery | Pathol. status | n | HL-G | AT | Present. status |
|-----|-----|------|---|---|----|---------|----------------|---------|----------------|---|------|----|----------------|
| 1   | 65  | R-C  | T1b| N1| a2 | TN      | PR            | Bp+Ax   | PR             | n0| 1b   | T: 3 | DFS (8y)       |
| 2   | 67  | R-AC | T2  | N1| a2 | TN      | cCR         | Bp+Ax   | pCR            | n0| 2b   | -    | DFS (9y)       |
| 3   | 31  | R-AB | T3  | N1| a1 | L-A     | PR            | Bp+Ax   | PR             | n1| 1b   | TC: 3 → HR | DFS (9y)       |
| 4   | 37  | R-C  | T1b| N1| a1 | L-B     | PR            | Bp+Ax   | PR             | n1| 1b   | TC: 3 → HR | DFS (8y)       |
| 5   | 40  | R-D  | T1b| N1| a1 | L-B     | cCR          | Bp+Ax   | n-pCR           | n0| 2b   | HR   | DFS (8y)       |
| 6   | 43  | L-CD | T2  | N1| a2+a3| L-B   | cCR         | Bp+Ax   | n-pCR           | n1| 2a   | TC: 3 → HR | DFS (8y)       |
| 7   | 46  | R-BD | T2  | N0| a1 | TN      | PR           | Bp+SNB  | PR             | n0| 1a   | TC: 3    | DFS (8y)       |
| 8   | 70  | R-BD | T2  | N1| a2 | TN      | cCR         | Bp+Ax   | pCR            | n0| 2b   | -      | DFS (7y)       |
| 9   | 40  | R-CD | T2  | N1| a2 | TN      | cCR         | Bp+Ax   | pCR            | n0| 1b   | -      | DFS (7y)       |
| 10  | 58  | L-C  | T2  | N1| a1 | TN      | CCR         | Bp+Ax   | n-PCR           | n1| 2a   | nab-PTX  | DFS (7y)       |
| 11  | 64  | R-C  | T2  | N1| a3 | L-A     | PR            | Bp+Ax   | PR             | n0| 2a   | -      | DFS (6y)       |
| 12  | 49  | R-A  | T1b| N0| a2 | TN      | CCR         | Bp+SNB  | PCR            | n0| 2a   | -      | DFS (6y)       |
| 13  | 69  | R-CD | T2  | N1| a2 | TN      | CCR         | Bp+Ax   | n-PCR           | n0| 2a   | -      | DFS (6y)       |
| 14  | 49  | L-C  | T2  | N1| a1 | L-B     | PR            | Bp+Ax   | PR             | n0| 1a   | ANA     | DFS (6y)       |
| 15  | 70  | L-AB | T2  | N1| a2 | TN      | CCR         | Bp+Ax   | PCR            | n0| 2b   | -      | DFS (6y)       |
| 16  | 69  | R-A  | T2  | N1| a2 | TN      | CCR         | Bp+Ax   | PCR            | n0| 2b   | -      | DFS (5y)       |
| 17  | 64  | R-CD | T2  | N1| a1 | L-B     | PR            | Bp+Ax   | PR             | n0| 1b   | EXE     | DFS (5y)       |
| 18  | 84  | R-C  | T3  | N1| a3 | TN      | PR            | Bp+Ax   | PR             | n0| 1b   | -      | DFS (5y)       |

T: tumor size, H.: histological type (invasive ductal carcinoma); a1: tubule forming type, a2: solid type, a3: scirrhous type
L-A: luminal-A, L-B: luminal-B, TN: triple negative, Bp: partial mastectomy, Ax: axillary dissection, SNB: sentinel node biopsy, HL-G: grade of the healed status, AT: post operative adjuvant therapy, TC: docetaxel + cyclophosphamide, HR: hormone therapy, n-PTX: nab-paclitaxel, EXE: exemestane, ANA: anastrosole, DFS: disease free survival, B/LN: bone and lymph nodes metastasis

Fig. 1 A representative patient treated with CEX-NAC: a 70-year-old woman, Rt-BD area, cT2, cN1, solid invasive ductal carcinoma (a2), triple-negative type, at first visit. The right breast tumor was characterized by internal medullary and marginal irregularity on mammography (LO region).

those who were node-positive after CEX-NAC. The treatment plan and schedule were decided by the attending doctors; there were no strict rules (Table 1). As of 2018, the average prognostic period for the present patients is 83.6 months (3-9 years). All patients who achieved pCR are recurrence-free, alive, and currently under observa-
Fig. 2 The right breast tumor was detected on CT (2a) and ultrasonography (2b; 32 × 28 mm). Right axillary lymph node swelling was visible on CT (2c) and in a microscopic view of biopsied tissues from the primary tumor (hematoxylin-eosin staining)—an invasive ductal (solid tubular) carcinoma (2d; ×400).

Discussion
The standard therapeutic strategy for localized breast cancer is adjuvant therapy or neoadjuvant chemotherapy (NAC) after surgery. In addition, histologic subtype and growth markers are evaluated to determine tumor characteristics\(^{14,16,19,39}\). Although the outcomes of these treatments do not substantially differ\(^{14,16,19,39}\), some studies found that patients who eventually achieved a pCR with NAC had satisfactory outcomes\(^{14,16,19,39}\). Breast-conserving surgery yielded significant benefits for patients with cT2 or worse tumors when surgery was successfully performed after NAC.

NAC is effective for TN cancer\(^{4,6,19}\); a frequently used regimen is 5-fluorouracil (5-FU) + epirubicin + cyclophosphamide (FEC) followed by weekly paclitaxel, including anthracycline and taxane\(^{1,3,4,6,14,16,18}\). The CRR is approximately 70% to 80%, and the pCR rate is approximately 20% to 40%\(^{1,3,4,6,18}\). With respect to histologic type, the pCR rate is high for solid invasive ductal carcinoma\(^{15,18}\).

Tolerability is a concern for chemotherapy. Moderate and severe adverse events after treatment with FEC followed by taxane for 6 months can affect patient quality of life, and such treatment is often disadvantageous for future breast cancer treatment\(^{1,3,4,6,14,16,38}\). Therefore, a regimen that results in good response and high tolerability is much desired.

Capecitabine (X), a constitutional isomer of 5-FU, is an oral pyrimidine fluoride drug that induces anti-tumor effects by using thymidine phosphorylase during the metabolic process. Because it does not take the form of 5-FU inside the intestinal tract or in blood, it theoretically induces less toxicity in blood and the digestive tract\(^{20,21,25,27,30,31}\). Concomitant use of capecitabine with drugs such as cyclophosphamide yielded higher chemical modulation than did monotherapy\(^{32,31,37}\). Moreover, some studies reported that concomitant therapy was more effective clinically than monotherapy\(^{22,24,26,33}\).

In CEX, the 5-FU in FEC is replaced by capecitabine\(^{30,34,36}\), the effectiveness of which was reported in the FinXX trial conducted by a group of medical professionals in Finland\(^{34,35,37}\). Saji et al. described its benefits in Japan\(^{33,38}\). In the present study, we administered a total of 4...
courses of CEX as NAC in our hospital. RR was achieved in 83.3% of patients, and the pCR rate was 33.8%. In particular, pCR was achieved in 44.4% of patients with TN or solid invasive ductal carcinoma. These outcomes are comparable to those of FEC and other regimens. All patients have continued follow-up assessments; some have been monitored for 8 years as of 2018. All patients classified as “pCR and node-negative in PR” are alive and free of recurrence, which suggests that control of lymph node metastasis is an important prognostic factor.

The present results suggest that treatment without taxane or 4-course treatment with anthracycline is adequate for some patients, when subtype and histologic characteristics are carefully considered. The present outcomes also suggest that concomitant use of capecitabine has synergistic effects. Moreover, pCR is a good prognostic predictor for most subtypes. However, pCR has not been established as an alternative endpoint for recurrence-free survival or overall survival in evaluating drug efficacy. Long-term observation and careful evaluation of outcomes are therefore necessary. Hematologic adverse events included neutropenia, which is common for FEC, which was classified as Grade 2 and resolved after treatment with granulocyte colony-stimulating factor. FN developed in 3 patients. All cases of non-hematologic toxicity, including digestive tract toxicity such as nausea and vomiting, were classified as Grade 2. Hand-and-foot syndrome was classified as Grade 1 because of the preset value of capecitabine and its schedule. Moreover, peripheral nerve disorders were rare, as taxane was not used. Thus, all patients treated with CEX therapy were able to complete 4 courses, suggesting that this regimen can help maintain patient quality of life.

**Conclusion**

This was a retrospective, single-center study. Therefore, larger clinical studies should investigate additional adjustments to the regimen, such as selection of indicated cases, optimal administration period, and administration of taxane agents.
Further improvement of genetic examinations will likely enable individualized treatment via appropriate drug selection in breast cancer treatment. The present findings suggest that CEX therapy as NAC might be an important option for individualized treatment. Although it was effective for TN breast cancer, the same benefits were not achieved for patients with luminal cancers.

Conflict of Interest: The authors declare no conflicts of interest.

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