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Prediction of pathological response to neoadjuvant chemotherapy in breast cancer patients by imaging

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ABSTRACT

Background: Diagnostic imaging is important for predicting the pathological response to chemotherapy during neoadjuvant chemotherapy (NAC) and for considering the surgical management with appropriate resection after NAC. This study was performed to examine the accuracy of the present radiological imaging for predicting the pathological complete response (pCR).

Methods: From 188 patients in our previous JONIE1 Study, a randomized controlled trial comparing chemotherapy with and without zoledronic acid for patients with human epidermal growth factor receptor 2-negative breast cancer, we evaluated 122 patients whose tumor size was examined by magnetic resonance imaging or ultrasound at three points: before NAC; after administering fluorouracil, epirubicin, and cyclophosphamide; and after NAC. The maximum tumor diameter was evaluated by magnetic resonance imaging or ultrasound. Tumor reduction ratios were calculated at the same three points. The association between the radiological clinical response and the pCR was examined.

Results: Among the 122 patients evaluated, there were 98 and 24 patients with luminal (Lum) and triple-negative (TN) subtypes, respectively. There were no patients who showed tumor progression after treatment. The radiological size of the tumors was finally reduced by an average of 58.4%. Clinical complete response and pCR were achieved in 22 (18.0%) and 15 (12.3%) patients, respectively. In the overall population ($n = 122$), the accuracy, sensitivity, and specificity for predicting pCR were 86.1%, 88.8%, and 66.7%, respectively. The negative predictive value and false-negative rate were 45.5% and 11.2%, respectively. According to subtypes, the accuracies were 83.7% and

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95.8% in Lum and TN, respectively. Negative predictive value and false-negative rate were markedly different between the Lum (29.4% and 13.5%) and TN subtypes (100% and 0%), respectively.

Conclusions: This randomized clinical trial demonstrated that NAC was safe for operable breast cancer patients with appropriate radiological monitoring. Radiological evaluation after NAC may be a reliable method for predicting pathological response in the TN subtype, but not in the Lum subtype.

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Introduction

Radiological assessment is important for estimating the required extent of surgical margins and the feasibility of breast-conserving surgery (BCS). This becomes more critical in patients with neoadjuvant chemotherapy (NAC) for clinical and research purposes. In NAC, it remains to be clarified whether the breast can be conserved safely with cosmetic satisfaction, as the main purpose of NAC is to reduce the tumor volume to allow BCS in patients with a relatively large tumor for BCS.

Interim radiological examinations are important because, although rare, patients whose tumors grow during NAC are occasionally encountered. An example is tumor shrinkage with an anthracycline-based regimen, but tumor regrowth with a taxane-based regimen. For these patients, the discontinuance of NAC and performing semi-emergent surgery may be considered as the strategy.

In recent years, NAC has been improved and has achieved pathological complete response (pCR) in 30%-50% of hormone receptor–negative breast cancers.[1] In the future, it may be possible to remove surgery with the accurate prediction of pCR, particularly in hormone receptor-negative subtypes. Based on the strategy for developing sentinel node biopsy aiming at omitting axillary dissection, the surgical resection of the breast tumor as the next step could be omitted if pCR can be predicted with a 90% accuracy and a 10% false-negative rate (FNR).[2] A feasibility study is therefore necessary to examine the efficacy of predicting pCR before surgery prior to performing an observational study without surgery.

In the present study, we examined the accuracy of radiological imaging for predicting pCR in a homogeneous cohort of patients from our previous randomized phase II NAC study who were treated with "fluorouracil, epirubicin, and cyclophosphamide" (FEC), followed by paclitaxel (PAC) exclusively for human epidermal growth factor receptor 2 (HER2)-negative breast cancer patients (JONIE1 Study).[3]

Methods

Study design and patients

We previously performed a randomized phase-2 trial in women with HER2-negative breast cancer to examine the efficacy of adding zoledronic acid (ZOL) to NAC by evaluating the pCR rate (JONIE1 Study).[3] Briefly, from March 2010 to June 2012, 188 patients were randomly assigned to either chemotherapy with ZOL ($n = 93$) or chemotherapy without ZOL ($n = 95$).[3]

The key eligibility criteria included histologically proven invasive luminal (Lum) or triple-negative (TN) breast cancer of clinical stage IIA to IIIB. The study investigators provided an information form that was approved by the institutional review board to all patients before enrollment to explain the trial and obtain voluntary written informed consent to participate in the study. The study was registered at the University Hospital Medical Information Network as UMIN000003261 (www.umin.ac.jp/english/).

Among the 188 patients enrolled in the JONIE1 Study, radiological measurements at all three points, namely before NAC, after FEC administration, and after NAC, were completed in 122 patients.

In the present study, changes in the tumor size and the correlation between radiological and pathological responses were examined in this cohort of 122 patients. The characteristics of the patients are shown in Table 1.

Treatment protocol

Four cycles of FEC100 (fluorouracil 500 mg/m^2, epirubicin 100 mg/m^2, and cyclophosphamide 500 mg/m^2) were administered by intravenous infusion every 3 wk followed by 12 cycles of PAC at 80 mg/m^2 by intravenous infusion once weekly. ZOL (4 mg) was administered four times every 3 wk with every FEC100 administration and three times every 4 wk during every PAC administration. Definitive surgery was performed 4 wk after the last PAC dose.

Radiological response measurements

In our previous JONIE1 Study, any imaging modality to evaluate the radiological response was allowed. In the present study, magnetic resonance imaging (MRI) or ultrasound (US) was used. The maximum tumor diameter was evaluated by MRI or US in each patient three times during NAC: before NAC, after FEC administration, and after NAC. Radiological response was evaluated as follows: clinical complete response (cCR), clinical partial response, clinical stable disease, and clinical progress disease (cPD). cCR by MRI was diagnosed if no gadolinium enhancement or an enhancement equal to or less than that of the glandular tissue was observed in any MRI phase. cCR by US was diagnosed in patients in whom no low-density mass was detected or only distortion remained.

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