President’s Address: History of Clinical Trials for Breast Cancer in Kyushu and Okinawa

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Nowadays, the treatment of breast cancer, especially medical therapy, is based on evidence; that is, evidence based medicine (EBM) is the standard. However, most of the evidence is acquired from clinical trials in western countries, and the evidence from Japan is rare.

Moreover, most of the medical treatment in the guidelines for breast cancer based on scientific grounds edited by the Japanese Breast Cancer Society issued this time refers to the data in western countries. However, in Japan, the evidence has started to be transmitted gradually from clinical trials of good quality in each district or all over Japan.

In the Kyushu and Okinawa districts, many clinical trials have been done since 1982, and some of them are now making progress. We introduce and explain the clinical trials which have been finished and published in the Kyushu and Okinawa districts by this time, discuss the ongoing clinical trials, and look back at the history of these trials (Fig 1).

Kyushu CAFT Study Group

The first clinical trial conducted in Kyushu was the 1st study of the adjuvant chemo-endocrine therapy for breast cancer (ACETBC) organization Nishinnihon Group, in 1982.

Since then, ACETBC has advanced to the 3rd trial, but we omit the details here because the results are already published.

The Kyushu cyclophosphamide, adriamycin, 5-FU, tamoxifen (CAFT) Study Group, in 1986, was the first clinical trial conducted largely in Kyushu except for the ACETBC. The CAFT Study Group has conducted three trials to date. The second of these was conducted at 37 participating institutions in September of 1988, and the aim was to compare CAF plus medroxyprogesterone acetate (MPA) therapy with CAF plus tamoxifen (TAM) for advanced or recurrent breast cancer (Fig 2).

Out of 119 registered cases, no significant differences were shown in the response rate, the duration of response or the survival time, but anorexia, nausea and vomiting were significantly less, and there was significantly more body weight gain and incidence of moon face in Arm B. Leucopenia was significantly inhibited in Arm B compared with Arm A, which indicated the myeloprotective effect of MPA. These results indicated that CAF + MPA therapy may be more advantageous than CAF + TAM therapy in advanced or recurrent breast cancer.

On the basis of these results, the third study started at 35 participating institutions in May of 1992.

The aim of this study was to find the optimal dose of MPA for advanced or recurrent breast cancer, and a randomized comparative study with a 1,200 mg group and 600 mg MPA group was carried out. Out of 118 registered cases, there were no significant differences in the response rate, the duration of response or the survival time. The results of this study revealed no differences in safety between the two arms, suggesting that MPA for combined use with CAF is fully effective at a dose of 600 mg.

Kitakyushu Collaborative Study Group

In the Kitakyushu area, the 1st collaborative study was conducted at 11 participating institutions to verify the administration method and recurrence-preventing effect of MPA as a postoperative adjuvant endocrine therapy for Stage III breast cancer in August of 1987 (Fig 3).
However, neither survival nor disease-free rates of the 92 analyzable patients were different between these treatment groups. Furthermore, the serum levels of MPA and cortisol had no correlation with survival or disease-free periods. However, the occurrence rate of moon face was significantly higher but the incidence of leucopenia less in the MPA group, showing the myeloprotective effect of MPA.

The next cooperative study was conducted at...
14 participating institutions in January of 1992 to evaluate the effectiveness of postoperative adjuvant chemo-endocrine therapy in node-positive breast cancer (Fig 4). The 119 registered patients were divided into two categories, \( n_1 \) (\( n = 1-3 \)) and \( n_1 \) (\( n \geq 4 \)). The \( n_1 \) patients were further subdivided into Group A and Group B, and the \( n_1 \) patients were placed into Group C or Group D. In the comparison between Group A and B, there was no significant difference in 5-year survival rate or 5-year disease-free survival rate. In the comparison between Group C and D, the results were the same.

The incidence of leucopenia in Group B was significantly higher than in Group A. Anorexia, nausea and alopecia occurred significantly more frequently in Group C than in Group D.

**Chu · Shikoku and Kyushu Toremifene Collaborative Study Group**

A study of high-dose toremifene (120 mg) for postmenopausal patients with advanced or recurrent breast cancer which was resistant to previous treatment or had relapsed, was conducted at 11 participating institutions in 1997, and of 11 evaluable cases, partial response rate (PR) was shown in 9.1% and long-term no change (NC) in 18.2%. Adverse effects were moderate and reversible. These results suggest that a high dose of toremifene might be effective for breast cancer resistant to TAM, MPA, aromatase inhibitor (AI), cyclophosphamide, or fluorouracil.

**UFT + Paclitaxel Study Group**

The Phase I study of UFT + weekly paclitaxel therapy for advanced or recurrent breast cancer was conducted in 2000, and UFT 400 mg/body, paclitaxel 170 mg/m\(^2\) became the recommended dose, with a response rate of 66.7%.

Based on the results, the Phase II trial has been underway at 7 institutions since March 2003.

**Kyushu Breast Cancer Study Group (KBS-SG)**

The Kyushu Breast Cancer Study Group (KBS-SG) started in March, 2000 at 10 participating institutions. First it examined weekly paclitaxel (C-1) as 2nd line treatment for advanced or recurrent breast cancer, including docetaxel resistant cases. It held a meeting to conduct large-scale clinical trials in the Kyushu and Okinawa districts in October, and it aimed at the spread of postoperative adjuvant therapy based on evidence-based medicine (EBM) in Kyushu, as follows: 1) Registration of all breast cancer cases (A); 2) Surveillance of postoperative adjuvant chemotherapy (B-
1); 3) AC followed by weekly paclitaxel (B-2) as the postoperative adjuvant chemotherapy for node positive breast cancer.

In July of 2002, we conducted increased dose studies of AC as postoperative adjuvant chemotherapy (B2), that is, adriamycin 50 mg/m², cyclophosphamide 500 mg/m², and in the newer clinical trials, weekly paclitaxel (B-3) as neoadjuvant therapy as well as 1st line therapy using paclitaxel combined with trastuzmab for advanced or recurrent breast cancer (C-2) and monotherapy with paclitaxel (C-3). We are now accumulating the cases (Table 1).

Since the appearance of capecitabine in July of 2003, Phase \( \geq \) trial using paclitaxel combined with capecitabine for advanced or recurrent breast cancer has also been conducted. At present, 59 institutions are participating in the clinical trials of KBC-SG in the Kyushu and Okinawa area.

We reported that the response rate was 30.4% in C-1 in 2002\(^8\) and it was 40% in C-3 in 2004\(^9\). Furthermore, the registrants into the B-1 arm were 55 institutions, with 2278 patients, as of November 2003\(^{10}\). As of October 2003 the B-2 arm had 41 cases, and the treatment accomplishment rate was 85.4%. The recurrence rate has been 20% up to now, but serious side effects have not been found and treatment on an outpatient basis is being carried out safely\(^{11}\).

**Epirubicin and Docetaxel (ET) Study Group**

A Phase I trial using epirubicin combined with docetaxel for advanced or recurrent breast cancer was conducted at 6 institutions in Kyushu and Tokyo in May of 2000, and the recommended dose in the no pre-treatment cases was decided to be 60 mg/m² for each, with a response rate of 66.7%\(^{12}\). From the results, Phase II study was conducted in July, 2002 following: 1) Neoadjuvant chemotherapy for primary breast cancer more than 3.1 cm in

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**Table 1. KBC-SG Study Group**

<table>
<thead>
<tr>
<th>Study Design</th>
<th>A: Registration of All Breast Cancer Cases</th>
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<tbody>
<tr>
<td>B-1: Surveillance of Postoperative Adjuvant Therapy</td>
<td>B-2: Postoperative Adjuvant Therapy (AC → Paclitaxel)</td>
</tr>
<tr>
<td>B-3: Neoadjuvant Chemotherapy (weekly Paclitaxel)</td>
<td>C-1: MBC-2nd line (weekly Paclitaxel)</td>
</tr>
<tr>
<td>C-2: MBC-1st line (Paclitaxel + Trastuzmab)</td>
<td>C-3: MBC-1st line (Paclitaxel)</td>
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</tbody>
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MBC: Metastatic Breast Cancer
AC: Adriamycin, Cyclophosphamide

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**Fig 4. Effectiveness of Postoperative Adjuvant Chemo-endocrine Therapy in Node-positive Breast Cancer.**
Table 2. Epirubicin and Docetaxel (ET) Study Group — Phase II Study —

Regimen: Epirubicin (60 mg/m²) + Docetaxel (60 mg/m²) q3w

Study Design

Neoadjuvant Chemotherapy: T ≥ 3.1 cm
Inflammatory Breast Cancer
Advanced or Recurrent Breast Cancer: 1st line

Patient Selection: Tumor size ≥ 1.0 cm

(1) Arm H-CEF (High)
CPA 500 mg/m² day 1
EPI 100 mg/m² day 1
5-FU 500 mg/m² day 1
4 courses

DOC 75 mg/m² day 1
4 courses

Surgery

± Hormonal Therapy ± RT (HT)

(2) Arm M-CEF (Moderate)
CPA 500 mg/m² day 1
EPI 75 mg/m² day 1
5-FU 500 mg/m² day 1
4 courses

DOC 60 mg/m² day 1
4 courses

Surgery

± HT ± RT

(2) Arm ET
EPI 60 mg/m² day 1
DOC 60 mg/m² day 1
4 courses

Surgery

EPI: Epirubicin
DOC: Docetaxel
RT: Radiation Therapy

size, 2) Inflammatory breast cancer, 3) 1st line therapy for advanced or recurrent breast cancer (Table 2).

According to the report of 2003, the response rate was 70.0%, 60.0% and 37.5% respectively for neoadjuvant therapy, inflammatory breast cancer and advanced or recurrent breast cancer, respectively. We are accumulating individual cases now, but a new clinical trial of neoadjuvant chemotherapy has been conducted since June, 2004 which is for resectable primary breast cancer of more than 1.0 cm in size. It includes 3 regimens as follows: 1) High dose CEF followed by docetaxel, 2) Moderate dose CEF followed by docetaxel, 3) Simultaneous use of epirubicin and docetaxel (Fig 5). A total of 75 institutions in the Kyushu and Okinawa districts are participating the ET Study Group now.

Capecitabine and Cyclophosphamide (XC) Study Group

Since the appearance of capecitabine in 2003, a Phase 1 trial using capecitabine combined with cyclophosphamide for pretreatment of advanced or recurrent breast cancer was conducted, and the trial for approval is now ongoing at the level 2 dose. The recommendation dose will be decided based on this study (Fig 6).

Kyushu and Okinawa Medical Therapy Study Group

Endocrine therapy has also been conducted since November, 2003. The clinical trial is a comparison of exemestane with anastrozol for post-menopausal recurrent breast cancer. It is a head to head comparison trial of exemestane and anastrozol as the 1st line therapy for post-menopausal patients who are hormone receptor positive or unknown (in unknown cases, disease free interval ≥ 2 years).
A variety of innumerable clinical trials are now carried out all over the world. However, there are few high evidence level results which are usable in actual practice. Moreover, there are very few cases participating in clinical trials, especially in Japan, and the evidence level is becoming low.

However, the data from clinical trials from Japan are necessary to the patients in our country, and from now on, through clinical trials of high quality in the Kyushu and Okinawa districts, we can offer more excellent medical treatment which gives priority to patients. We must make efforts to improve the survival rate of breast cancer in Japan.

**References**


