The Transition of Breast Cancer Treatment and Japan Clinical Oncology Group Research Over Two Decades

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The Japanese Breast Cancer Study Group (JABCSG) was established before the Japan Clinical Oncology Group (JCOG). The JABCSG became the JCOG Breast Cancer Group 20 years ago. The first chairman of the Breast Cancer Group was Dr Kaoru Abe (National Cancer Center Hospital). Since 1978, five doctors have chaired the Breast Cancer Group. Sixteen clinical trials (eight phase III and eight phase I/II) have been conducted by the Breast Cancer Group since 1985. The Breast Cancer Group was restructured in 2010, and in June 2011 a new clinical trial (JCOG 1017) was initiated. Standard treatment for breast cancer (surgery, radiotherapy and systemic therapy) has changed dramatically over the last two decades. This review describes the transition of breast cancer treatment along with the history of JCOG research in this setting.

Key words: JCOG – Breast Cancer Group – clinical trial

INTRODUCTION

The Japanese Breast Cancer Study Group (JABCSG) was established before the Japan Clinical Oncology Group (JCOG). The JABCSG became the JCOG Breast Cancer Group 20 years ago. The first chairman of the JCOG Breast Cancer Group was Dr Kaoru Abe (National Cancer Center Hospital). Since 1978, five doctors have chaired the Breast Cancer Group (Table 1). Sixteen clinical trials (eight phase III and eight phase I/II) have been conducted by the Breast Cancer Group since 1985 (Table 2). Unfortunately, no new clinical trials have been conducted by JCOG during the last 5 years because of the establishment of other clinical trial groups in Japan. However, the Breast Cancer Group was restructured in 2010 and a new clinical trial (JCOG 1017) was initiated in June 2011.

Standard treatment (surgery, radiotherapy and systemic therapy) for breast cancer has changed dramatically over the last two decades. This review describes the transition of breast cancer treatment along with JCOG research in the field.

SURGERY

In 1985, the standard surgical procedure for breast cancer in Japan was radical mastectomy or modified radical mastectomy, as breast-conserving surgery (partial dissection plus radiotherapy) had not yet been introduced. The use of radical mastectomy decreased after publication of the results from a clinical trial comparing radical mastectomy and modified radical mastectomy (1,2). Since 1990, the use of breast-conserving surgery has increased the following results from clinical trials in the USA and Europe that compared mastectomy and partial dissection plus radiotherapy (3,4). Currently, breast-conserving surgery is used in 60% of patients with early breast cancer (EBC) in Japan.

The pattern of axillary surgery has also changed dramatically since 1985. Until 2005, axillary dissection was a standard treatment for patients with EBC regardless of involved lymph node metastasis. Worldwide, including Japan, the current gold standard treatment approach avoids axillary dissection in patients with node-negative EBC, with clinical status evaluated using sentinel lymph node biopsy (5,6).
Axillary dissection is now avoided in 70% of all patients with EBC in Japan. Unfortunately, no clinical trials of surgical procedures have yet been conducted by JCOG in patients with EBC.

RADIOTHERAPY

In 1985, radiotherapy was used to control symptoms, including bone pain, and as local control for chest wall and brain metastases in patients with advanced or metastatic breast cancer (MBC). After 1990, radiotherapy became a standard treatment for patients with EBC after partial dissection of the breast. External radiotherapy (50 Gy) after surgery is now strongly recommended by guidelines across the world, including Japan (7). Furthermore, new treatments, such as intraoperative external radiation (8) or accelerated partial breast irradiation (9) after conservative surgery, are now being evaluated in trials across the world including Japan. A new clinical trial (JCOG 0906; single-arm phase II trial) involving a decreased frequency of external radiation is currently being conducted by the JCOG Radiation Oncology Group. Chest wall and supraclavicular radiation after mastectomy has been used as a standard procedure since 2005 in patients with EBC who have more than three positive axillary lymph nodes (10). A multimodality approach (surgery, radiation and systemic therapy) is considered very important to improve outcomes and quality of life after initial treatment in patients with EBC. The JCOG clinical trial of multimodality therapy (JCOG 0306) was performed 6 years ago.

Table 2. Clinical trials conducted by the JCOG Breast Cancer Group over the last two decades

<table>
<thead>
<tr>
<th>JCOG no.</th>
<th>Phase</th>
<th>Breast cancer setting</th>
<th>Enrollment start date</th>
<th>Enrollment end date</th>
<th>No. of registered patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>0306</td>
<td>II</td>
<td>Early</td>
<td>Jun 2004</td>
<td>Apr 2005</td>
<td>108</td>
</tr>
<tr>
<td>8808</td>
<td>III</td>
<td>Metastatic</td>
<td>Dec 1988</td>
<td>Dec 1991</td>
<td>233</td>
</tr>
<tr>
<td>9114</td>
<td>III</td>
<td>Metastatic</td>
<td>Feb 1992</td>
<td>Mar 1996</td>
<td>456</td>
</tr>
<tr>
<td>9802</td>
<td>III</td>
<td>Metastatic</td>
<td>Jan 1999</td>
<td>May 2003</td>
<td>441</td>
</tr>
<tr>
<td>0111</td>
<td>III</td>
<td>Metastatic</td>
<td>1 Jun 2002</td>
<td>Jun 2004</td>
<td>13</td>
</tr>
<tr>
<td>1017</td>
<td>III</td>
<td>Advanced</td>
<td>Jun 2011</td>
<td>Ongoing</td>
<td></td>
</tr>
<tr>
<td>8504</td>
<td>RII</td>
<td>Metastatic</td>
<td>Dec 1985</td>
<td>Jan 1988</td>
<td>125</td>
</tr>
<tr>
<td>9102</td>
<td>II</td>
<td>Metastatic</td>
<td>Nov 1993</td>
<td>51</td>
<td></td>
</tr>
<tr>
<td>9108</td>
<td>I/II</td>
<td>Metastatic</td>
<td>Dec 1991</td>
<td>Mar 1994</td>
<td>30</td>
</tr>
<tr>
<td>9503</td>
<td>II</td>
<td>Metastatic</td>
<td>Oct 1995</td>
<td>Mar 1997</td>
<td>18</td>
</tr>
<tr>
<td>9006</td>
<td>II</td>
<td>Metastatic</td>
<td>Feb 1991</td>
<td>Jun 1997</td>
<td>63</td>
</tr>
<tr>
<td>9602</td>
<td>I</td>
<td>Metastatic</td>
<td>Oct 1996</td>
<td>May 1998</td>
<td>7</td>
</tr>
<tr>
<td>9208</td>
<td>III</td>
<td>Early</td>
<td>May 1993</td>
<td>Mar 1997</td>
<td>97</td>
</tr>
<tr>
<td>9401</td>
<td>III</td>
<td>Early</td>
<td>Oct 1994</td>
<td>Jul 1999</td>
<td>129</td>
</tr>
<tr>
<td>9404</td>
<td>III</td>
<td>Early</td>
<td>Oct 1994</td>
<td>Jul 1999</td>
<td>169</td>
</tr>
</tbody>
</table>

Advanced, primary breast cancer with distant metastasis; R, randomized; BC, breast cancer.

Axillary dissection is now avoided in 70% of all patients with EBC in Japan. Unfortunately, no clinical trials of surgical procedures have yet been conducted by JCOG in patients with EBC.

JCOG 0306 Trial

The JCOG 0306 trial was conducted to evaluate the efficacy and safety of neoadjuvant chemotherapy followed by radiotherapy of the whole breast in patients with EBC. The primary endpoint was the pathological complete response (pCR) rate and secondary endpoints were adverse events, clinical complete response (CR) rate, percentage of patients undergoing breast-conserving surgery, relapse-free survival (RFS) and overall survival (OS). Patients with Stages I–IIIA (tumor ≤2 cm and ≤5 cm) breast cancer received initial chemotherapy [4 cycles of doxorubicin and cyclophosphamide followed by 12 cycles of weekly paclitaxel] and sequential radiotherapy (whole breast 45 Gy plus 10 Gy boost). The efficacy of neoadjuvant chemotherapy and radiotherapy was evaluated using pathological findings from specimens obtained by radical surgery. Unfortunately, after results from a planned interim analysis, this trial was halted early because a pCR was not reported in the first seven patients, so meeting an early stopping rule. However, the planned number of patients had already been enrolled at the time of trial discontinuation because of rapid recruitment, and final data were reported at the 2010 meeting of the American Society of Clinical Oncology (11).

Between June 2004 and April 2005, 108 patients were enrolled. The pCR rate in the whole population was 36%. The pCR rate was 57% in patients with hormone receptor (HR)-negative and human epidermal growth factor receptor 2 (HER2)-positive tumors, and it was 52% in patients with triple-negative disease. While 7% of patients with HR-negative HER2-positive tumors experienced disease progression, a higher incidence of recurrence (24%) was reported in patients with triple-negative disease during the follow-up of 4.5 years. The breast-conserving surgery rate was 91% (96/106). One patient underwent debridement of...
radiation-associated necrosis 3 months after lumpectomy. Other toxicities were mild to moderate (11).

Preoperative sequential chemoradiation therapy did not increase the risk of operative complications and was associated with a high rate of breast-conserving surgery, even though the expected pCR rate was not achieved. Selection of a subgroup of patients with EBC might be the next step towards realizing the aim of non-surgical treatment for EBC. The final publication from this study is currently being prepared.

SYSTEMIC THERAPY

Systemic agents for breast cancer were limited in 1985. Tamoxifen and oral cyclophosphamide were usually used after surgery in patients with EBC regardless of estrogen receptor (ER) status. Data on the clinical benefit of adjuvant therapy were limited at the time. Bonadonna et al. (12) were the first to report on this treatment approach. Their trial established the benefit of adjuvant systemic therapy by comparing patients who received cyclophosphamide, methotrexate, and 5-fluorouracil as adjuvant therapy with a group who received no adjuvant therapy.

METASTATIC BREAST CANCER

In Japan in the 1980 s, hormone therapy, such as tamoxifen and medroxyprogesterone acetate (MPA), and cytotoxic drugs, such as doxorubicin and oral 5-fluorouracil, were sometimes used in patients with advanced breast cancer or MBC with distant metastasis. Following the approval of docetaxel in 1998 and paclitaxel in 1999, the taxanes have become key drugs in MBC treatment alongside the anthracyclines.

JCOG 8504 TRIAL (JABCSG-I)

JCOG 8504 was the first clinical trial conducted by the JCOG Breast Cancer Group in patients with MBC and was started in 1985. The objective of this phase II trial was to compare the efficacy of regimens including doxorubicin or mitomycin C (MMC) in patients with MBC. Endpoints were response rate, duration of response, time to progression, OS and adverse events. Eligible patients had ER-positive or unknown status MBC; a total of 125 patients were enrolled in this trial. Patients randomized to group A were treated with an initial regimen of tamoxifen + cyclophosphamide + MMC. After progression, the treatment regimen was changed to Halotestin (HAL) + tegafur + doxorubicin. Patients in group B received an initial regimen of HAL + tegafur + doxorubicin, which was changed to tamoxifen + cyclophosphamide + MMC after progression.

There were no differences in patient characteristics between the two groups. The tumor response rates with initial therapy were 33.9 and 47.8% in groups A and B, respectively; the response rates to secondary therapy were 33.3 and 23.5%, respectively. There was no correlation between the response rates for initial and secondary therapy. OS was significantly better in group B than group A: median survival was 16.4 months in group A and 41.2 months in group B. The JCOG 8504 trial thus indicated that the doxorubicin-containing regimen was more effective than the MMC-containing regimen as first-line treatment for patients with MBC.

JCOG 8808 TRIAL (JABCSG-II)

The multi-institutional randomized phase III JCOG 8808 trial (Tables 2 and 3) was conducted on the basis of the results from JCOG 8504. In 1988, the standard first-line treatment regimen for patients with MBC was doxorubicin + cyclophosphamide + tamoxifen (ACT). The use of methotrexate and the taxanes (paclitaxel and docetaxel) had not been approved in this treatment setting at that time. The objective of the JCOG 8808 trial was to compare the efficacy and safety of ACT with doxorubicin + cyclophosphamide + MPA (ACM) in patients with MBC. Endpoints were response rate, duration of response, time to progression, OS, adverse events and quality of life. A total of 233 patients were enrolled in this study. Baseline characteristics of patients were well balanced between the two groups. The tumor response rate was 61.3% in the ACT group and 51.4% in the ACM group. The incidence rates for anemia, leukocytopenia and nausea and vomiting were significantly lower in the ACM group compared with the ACT group. Conversely, body weight gain was significantly higher in the ACM group. There was a favorable trend in the OS rate for the ACT group compared with the ACM group. On the basis of these data, the ACT regimen was judged to be better than the ACM regimen as first-line therapy for patients with MBC.

Multivariate regression analysis of data from JCOG 8808 was performed to identify significant prognostic factors and a prognostic index was constructed (13). Prior adjuvant chemotherapy, the presence of positive distant lymph nodes, liver metastases, elevation of serum lactate dehydrogenase and shorter disease-free interval were identified as important prognostic factors in patients with MBC. The prognostic index enables patients with MBC to be stratified into three risk groups (low, intermediate and high risk) for survival and its use is worth considering in future clinical trials (13).

JCOG 9114 TRIAL

The JCOG 9114 trial (Tables 2 and 3) was initiated on the basis of the results from JCOG 8808. When JCOG 9114 commenced in 1992, standard first-line therapy in patients with MBC was still ACT; however, the optimal use of MPA was unclear in this setting.

The JCOG 9114 trial was thus conducted to determine the optimal use of MPA in patients with MBC. The efficacy and safety of three regimens [ACT alone versus ACT + low-dose MPA (ACTM-low) versus ACT + high-dose MPA (ACTM-high)] were compared in patients with MBC. Primary endpoints were response rate, duration of response
and adverse events; secondary endpoints were quality of life and OS. A total of 455 patients were enrolled in this study. The response rate was 53% (241/455) and the median 2-year survival rate was 53.4%. The median survival was 778 days (range, 710–879 days) after randomization. During protocol treatment, one, six and three patients died in the AC, single-agent docetaxel and AC-D groups, respectively (one-sided log-rank test; \( P = 0.13 \) for AC versus single-agent docetaxel; \( P = 0.14 \) for AC versus AC-D). There was no difference in TTF among the three groups. The researchers concluded that there was a favorable trend in OS for single-agent docetaxel compared with AC in this setting (15).

**JCOG 0111 Trial**

The objective of the JCOG 0111 trial (Tables 2 and 3) was to compare the efficacy and safety between weekly and 3-weekly paclitaxel in patients with MBC. The primary endpoint was response rate and secondary endpoints were adverse events, PFS and OS. Recruitment of patients into JCOG 0111 was hampered by the delayed initiation of this trial, despite the fact that investigators demonstrated interest in the trial design. Some data were published, but it took a long time to complete the protocol due to the prolonged JCOG confirmation process. The study investigators concluded that the weekly paclitaxel regimen should be a standard treatment in MBC. However, the trial was stopped after 13 patients had enrolled and full data were not published.

**JCOG 1017 Trial**

For 10 years after the JCOG 0111 trial, the JCOG Breast Cancer Group conducted no clinical trials in patients with MBC. Many agents are now available for the treatment of MBC including hormone therapy [e.g. luteinizing hormone-

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Table 3. Design and key results of phase III clinical trials conducted by the JCOG Breast Cancer Group over the last two decades

<table>
<thead>
<tr>
<th>JCOG no.</th>
<th>Eligibility criteria</th>
<th>Standard arm</th>
<th>Experimental arm(s)</th>
<th>Primary endpoint</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>8808</td>
<td>MBC, first line</td>
<td>ACT</td>
<td>ACM</td>
<td>RR</td>
<td>ACT &gt; ACM</td>
</tr>
<tr>
<td>9114</td>
<td>MBC, first line</td>
<td>ACT</td>
<td>ACT + low-dose MPA</td>
<td>RR, duration of response, AEs</td>
<td>Unclear not published</td>
</tr>
<tr>
<td>9802</td>
<td>MBC, first line, resistant to endocrine therapy</td>
<td>AC→DOC</td>
<td>DOC→AC alternating AC and DOC</td>
<td>TTF</td>
<td>No difference among the three arms</td>
</tr>
<tr>
<td>0111</td>
<td>MBC, first line, resistant to endocrine therapy</td>
<td>3-weekly paclitaxel</td>
<td>Weekly paclitaxel</td>
<td>RR</td>
<td>Stopped by late enrollment</td>
</tr>
<tr>
<td>1017</td>
<td>Advanced BC (stage IV)</td>
<td>Systemic therapy alone without primary resection</td>
<td>Primary resection after initial therapy</td>
<td>OS</td>
<td>Ongoing</td>
</tr>
<tr>
<td>9208</td>
<td>Stages I–III BC, ≥10 positive LNs</td>
<td>CAF→TAM</td>
<td>CAF→HDC with CPA + thiopeta→TAM</td>
<td>RFS</td>
<td>No benefit with HDC</td>
</tr>
<tr>
<td>9401</td>
<td>Postmenopausal BC, &lt;10 positive LNs</td>
<td>ACT</td>
<td>TAM</td>
<td>OS</td>
<td>Unclear not published</td>
</tr>
<tr>
<td>9404</td>
<td>Premenopausal BC, &lt;10 positive LNs</td>
<td>ACT</td>
<td>UFT + TAM</td>
<td>OS</td>
<td>Unclear not published</td>
</tr>
</tbody>
</table>

AC, doxorubicin + cyclophosphamide; ACM, doxorubicin + cyclophosphamide + MPA; ACT, doxorubicin + cyclophosphamide + TAM; AE, adverse event; CAF, cyclophosphamide + doxorubicin + 5-fluorouracil; DOC, docetaxel; HDC, high-dose chemotherapy; LN, lymph node; MBC, metastatic breast cancer; MPA, medroxyprogesterone acetate; OS, overall survival; RFS, relapse-free survival; RR, response rate; TAM, tamoxifen; TTF, time to treatment failure; UFT, tegafur-uracil.
releasing hormone (LHRH) analogs, selective ER modulators, aromatase inhibitors and MPA, targeted therapy (e.g., trastuzumab and lapatinib) and cytotoxic drugs (e.g., anthracycline-containing regimens, taxanes, vinorelbine, oral 5-fluorouracil, gemcitabine, eribulin and nab-paclitaxel). The choice of regimen for patients with MBC should be based on a variety of factors including molecular subtype, symptoms caused by recurrent or metastatic lesions, previous treatment (adjuvant therapy), duration of disease-free interval (from initial treatment to recurrence) and patient preference. Many clinical trials of new agents are currently ongoing and we are conducting a new trial in patients with advanced breast cancer and distant metastasis (JCOG 1017).

The objective of the randomized phase III JCOG 1017 trial (Tables 2 and 3) is to compare the efficacy of primary tumor resection plus systemic therapy versus systemic therapy alone in patients with advanced breast cancer and distant metastasis. Initial treatments are selected according to molecular subtype of the primary site and choices include hormone therapy (aromatase inhibitor or LHRH analog + tamoxifen) and chemotherapy (weekly paclitaxel) with/without targeted therapy (trastuzumab). After 3 months, tumor response is estimated by clinical evaluation. All patients except those who have progressed after initial therapy are then randomized to either undergo primary tumor resection or to continue systemic therapy without resection. The primary endpoint is OS and secondary endpoints are local recurrence rate, local control rate and effect on distant metastasis after resection of the primary site. Enrollment commenced in June 2011 and the target sample size is 455 patients.

**OTHER PHASE I/II MBC TRIALS**

Four small phase I/II JCOG trials (9107, 9108, 9113 and 9503) were conducted in patients with MBC. Unfortunately, none of the regimens in these trials were investigated in phase III trials because of changes in standard MBC therapy, as previously described.

The phase II JCOG 9107 trial evaluated the efficacy and tolerability of high-dose epirubicin (130 mg/m²) + cyclophosphamide (1000 mg/m²) with granulocyte colony-stimulating factor (G-CSF) every 3 weeks in patients with HR-negative MBC (16).

A total of 51 patients were enrolled in JCOG 9107. The response rate was 64% [95% confidence interval, 50.1–75.9%; CR, 14%; partial response (PR), 50%]. No treatment-related deaths were reported but symptomatic and acute hematologic toxicities (grade ≥3) occurred frequently: leukopenia, 98%; thrombocytopenia, 42%; nausea and vomiting, 56% and alopecia, 12%. The incidence of cardiotoxicity was low: arrhythmia (grade ≥2) was observed in 8% of patients and a slight decrease of ejection fraction index (grade ≥2) was reported in 2%. The median follow-up was 37.2 months (range, 24.6–51.5 months) and the median survival was 17.4 months (16).

The JCOG 9108 trial was a phase I dose-finding study of continuous vinorelbine infusion for 5 days in 26 patients with MBC. The endpoint was determination of the recommended dose based on dose-limiting toxicity and the maximum tolerable dose. A vinorelbine dose of 40 mg/m² was recommended on the basis of this trial.

JCOG 9113 was a phase I/II trial of continuous intra-arterial infusion of 5-fluorouracil using an implanted reservoir to treat liver metastases in patients with breast cancer (17). The objectives of this phase I/II trial were to determine the recommended dose of 5-fluorouracil and to evaluate its efficacy and safety.

In the phase I part of this trial, patients received doxorubicin 30 mg/m²/day on Days 1 and 8 of each 28-day cycle; cohorts of patients received escalating doses of 5-fluorouracil (120, 200, 300 and 400 mg/m²/day) as a continuous infusion from Day 1 to 14. The dose-limiting toxicity was thrombocytopenia. The maximum tolerable dose was determined as 5-fluorouracil 400 mg/m²/day and thus the dose recommended for use in the following phase II trial was 5-fluorouracil 300 mg/m²/day. Nine patients were registered in the phase II trial. The response rate was 50% in the eight eligible patients with liver metastasis. The most common adverse events were alopecia, gastrointestinal symptoms and bone marrow suppression. The median duration of response was 5.8 months (range, 1–23 months) and the median survival was 25.3 months (range, 6.2–54.7 months) (17).

Since the JCOG 9113 trial, only one randomized phase II trial (18) and a number of case reports have been published by JCOG Breast Cancer Group investigators on continuous intra-arterial chemotherapy. No randomized clinical trials have compared continuous intra-arterial chemotherapy with systemic chemotherapy using venous infusion. The most recent treatment guidelines do not recommend the use of continuous intra-arterial chemotherapy using an implantable reservoir in patients with MBC and liver metastasis because of the imbalance between benefit and risk (19).

The other phase II study conducted by the Breast Cancer Group was JCOG 9503. The objective of this trial was to evaluate the efficacy and safety of MMC + vinblastine in patients with MBC who were refractory to doxorubicin, tamoxifen and MPA. The primary endpoint was response rate and secondary endpoints were adverse events, PFS and OS. Consensus on the trial design was not achieved among all investigators, which resulted in delayed initiation of recruitment. This trial was subsequently discontinued and no data are available.

**HIGH-DOSE CHEMOTHERAPY**

Three clinical trials of high-dose chemotherapy (HDC) were conducted by the JCOG Breast Cancer Group. Two phase I/II trials (JCOG 9006 and 9602) were conducted in patients with MBC and one phase III trial (JCOG 9208) evaluated postoperative HDC in patients with high-risk EBC.
JCOG 9006 Trial

The purpose of the JCOG 9006 trial was to evaluate the efficacy and safety of consolidation therapy with autologous hematopoietic stem cell transplantation (AHSCT) following induction therapy in patients with MBC. The induction therapy was cyclophosphamide 1000 mg/m² + epirubicin 130 mg/m² on Day 1 with G-CSF on Day 2. The consolidation chemotherapy regimen was cyclophosphamide 2000 mg/m² + thiotepa 200 mg/m² with AHSCT and G-CSF. A total of 63 patients were enrolled in the induction therapy phase and 41 patients were enrolled in the consolidation therapy phase. The response rate was 51.6% (32/62; CR, 7 patients; PR, 25 patients) after the induction phase. The 3-year survival rate was 31.2%. No unexpected adverse events were reported.

JCOG 9602 Trial

JCOG 9602 was a phase I dose-finding trial of doublet HDC with AHSCT in patients with MBC conducted at a single institution. Cyclophosphamide 6000 mg/m² + thiotepa 600 mg/m² was used as the HDC regimen in the first cycle. Patient cohorts were then allocated to receive escalating dose levels in the second cycle: cyclophosphamide 3000 mg/m² + thiotepa 300 mg/m² at level 1, cyclophosphamide 4500 mg/m² + thiotepa 450 mg/m² at level 2 and cyclophosphamide 6000 mg/m² + thiotepa 600 mg/m² at level 3. Seven patients were enrolled in the level 1 cohort but the trial was stopped before the level 2 cohort commenced. Unfortunately, final data from this study were not published.

JCOG 9208 Trial

The JCOG 9208 trial (Tables 2 and 3) was a randomized controlled trial to evaluate the efficacy of postoperative HDC as consolidation treatment in high-risk breast cancer (20). The primary endpoint was RFS and secondary endpoints were OS and toxicity. Patients aged <56 years with stages I–IIIB breast cancer involving >10 axillary lymph nodes were eligible and 97 patients were enrolled. All major characteristics were well balanced between the treatment arms. Forty-eight patients in the standard-dose arm received six cycles of cyclophosphamide, doxorubicin and 5-fluorouracil (CAF) followed by tamoxifen. Forty-nine patients were assigned to HDC with cyclophosphamide and thiotepa after six cycles of CAF followed by tamoxifen. HDC was well tolerated and no treatment-related mortality was reported. In the intent-to-treat population, 5-year RFS was 37% in the standard-treatment arm (n = 47 eligible patients) versus 52% in the HDC arm (n = 48 eligible patients) (P = 0.17). The 5-year OS rates (all randomized patients) were 62 and 63% in the standard-treatment arm and HDC arm (P = 0.78), respectively. No increased benefit with HDC was demonstrated in terms of RFS or OS (20).

The phase II JCOG 9006 trial enrolled 42 patients and the phase I JCOG 9602 trial enrolled seven patients. Responsibility for both trials was moved from the JCOG Breast Cancer Group to the Hematopoietic Oncology Group after enrollment was completed. Although no longer under our remit, it is of interest to note that no positive data have subsequently been reported from HDC trials in this setting (21). Therefore, Japanese and international guidelines do not recommend HDC in patients with EBC or advanced breast cancer (22).

(NEO)Adjuvant Systemic Therapy

Many reports have been published since 1985 on adjuvant and neoadjuvant systemic treatments for breast cancer. Meta-analyses of large randomized clinical trials have been performed every 5 years by the EBC Trialists' Collaborative Group. Furthermore, a consensus conference on clinical questions in EBC treatment has been held every 2 years. Two clinical trials of (neo)adjuvant treatments (JCOG 9401 and JCOG 9404) have been conducted by JCOG but neither has been able to establish a standard therapy in Japanese patients with EBC.

JCOG 9401 Trial

The objective of the JCOG 9401 trial (Tables 2 and 3) was to compare outcomes in postmenopausal women with primary breast cancer and <10 positive lymph nodes who were randomized to one of two regimens (ACT or tamoxifen alone). The primary endpoint was OS and the secondary endpoint was disease-free survival. Planned enrollment was 220 patients. However, this trial was halted prematurely because patient registration was very slow and fewer events occurred than expected. At termination, 129 patients had been enrolled. The 3-year OS rate was 92.8% in both groups.

JCOG 9404 Trial

The JCOG 9404 trial was conducted to compare outcomes between two regimens (ACT versus tegafur-uracil + tamoxifen) in premenopausal women with breast cancer and <10 positive lymph nodes. The primary endpoint was OS and the secondary endpoint was disease-free survival. It was planned to enroll 330 patients. As was the case for JCOG 9401, the JCOG 9404 trial was halted prematurely because patient registration was very slow and fewer events occurred than expected. Only 169 patients were enrolled in this study. The 3-year OS rate was 89.9% in both groups.

Conclusion

Treatment strategies in breast cancer have evolved dramatically in the last two decades on the basis of data from large...
clinical trials conducted worldwide. Unfortunately, to date, none of the clinical trials conducted by the JCOG Breast Cancer Group have provided positive data to support new treatment options. However, it should not be forgotten that negative trial results are of equal importance to positive ones as they allow us to rule out unsuitable treatments. Furthermore, data from JCOG 8808 were used to construct a prognostic index for survival in MBC (13). We are hopeful that our new clinical trials will provide evidence that will contribute towards establishing more effective standard treatments for breast cancer in the future.

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**Conflict of interest statement**

None declared.

**References**