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Updated results of the assessment of the role of her-2 overexpression as a predictive factor to neoadjuvant, anthracycline-containing chemotherapy in locally-advanced breast cancer (LABC)

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Objective: to assess, whether HER-2 overexpression has any influence to response to neoadjuvant chemotherapy, containing anthracyclines. Secondary endpoint was association of HER-2 positivity with time to progression (TTP) and overall survival (OS) after neoadjuvant treatment of LABC.

Methods: ninety-six consecutive patients (pts) with LABC were treated with anthracycline-containing neoadjuvant chemotherapy and underwent radical surgery between 12.2002 and 12.2003.HER-2 expression was determined by routine clinical laboratory assesment. Tumors with 3+ immunohistochemistry staining intensity or gene amplification by fluorescent in situ hybridization were considered HER-2 positive. Patients were divided into 2 groups according to HER-2 expression: I – negative: N = 50; II-positive: N = 46.Response to neoadjuvant chemotherapy was assesed by physical, pathologic and imaging examination; TTP and OS by Kaplan-Meier analysis.

Results: forty-six (47%) pts had HER-2 positive tumors. Median age was: I – 52 (35–74), II – 53 (35–76) yrs. ⩾T2 tumors: I – 34 (68%), II – 33 (72%) pts. Most common chemotherapy was AC regimen: I – 36 (72%), II – 34 (74%) pts; doxorubicin + docetaxel (AT) received: I – 7 (14%), II – 3 (7%); other, such as FAC, FEC, T/ET or doxorubicin monotherapy were rare: I – 7 (14%), II – 9 (19%) pts altogether. At least 4 cycles of chemotherapy received: I – 48 (96%), II – 43 (93%) pts. The clinical response rate (complete response [CR] and partial response [PR]) was: I – 58% (29/50), II – 72% (33/46), CR I – 16% (8/50), II – 17% (8/46) pts. Pathological CR was achieved in: I – 6% (3/50), II – 6.5% (3/46) pts. Median time of follow-up was 23 months. Twenty-seven relapses were noted: I – 12 (24%), II – 15 (33%). Median TTP was I – 22 months, II – 16 months. Time for OS has not been reached yet.

Conclusion: there was a tendency to better response for HER-2 positive tumors. We found no significant correlation between TTP and HER-2 overexpression. More patients and longer follow-up is needed to draw further conclusions, but better response and more relapses in HER-2 positive group suggest that anthracycline-containing chemotherapy followed by trastuzumab may be a better therapeutic option for these patients. The analysis of further cases included to analysis since 01.2004 and results of follow-up of remaining patients will be presented.

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Relative dose intensity (RDI) relevance in adjuvant CMF chemotherapy of breast cancer

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Background: Intensity of adjuvant chemotherapy in breast cancer patients is considered a prognostic factor, although published results are conflicting. In this study we retrospectively analyzed the impact of RDI in early breast cancer patients administered adjuvant CMF.

Material and Methods: Between 1990 and 1997 a total of 285 consecutive breast cancer patients received adjuvant CMF chemotherapy (100 mg/m^2 cyclophosphamide p.o. on days 1–14, 40 mg/m^2 i.v. methotrexate on days 1 and 8, and 600 mg/m^2 i.v. 5-fluorouracil on days 1 and 8, q. 4 weeks, for a total of six cycles). Twenty patients were excluded from the analysis due to inadequate number of cycles actually administered (⩽4). Postoperative radiotherapy and endocrine therapy was applied in 16% and 10% of patients, respectively. Median age was 46 years (range, 30–62 years), 66% of patients had nodal involvement, 82% of tumors were ductal carcinomas, and 40% were grade 3. The administered dose intensity of cyclophosphamide, methotrexate and 5-fluorouracil relative to the planned dose intensity was calculated for each patient. Univariate and multivariate survival analysis was performed with log rank test and Cox proportional hazards model with the use of Wald's statistics to test each variable in backward-stepwise regression. RDI was categorized only after the final model had been found.

Results: Median follow-up was 7.7 years (range 4.0–11.6 years). Actuarial survival probability at 5 and 10 years was 76% and 62%, respectively. The number of involved axillary lymph nodes was the strongest predictor of outcome. Median RDI for cyclophosphamide, methotrexate and 5-fluorouracil was 83%, 77% and 93%, respectively. Median average dose intensity for all drugs was 86%. RDI of 78% and more was significant predictor of overall survival, with 0.6 hazard risk of death (95% CI 0.37–0.99; p = 0.045) and 0.57 hazard risk of relapse (95% CI 0.35–0.92; p < 0.001).

Conclusions: RDI is a strong and independent predictor of overall survival and disease-free survival in breast cancer patients administered adjuvant CMF chemotherapy, with 78% being the best cut-off discriminating value.

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Pathological response to preoperative concurrent chemoradiotherapy for breast cancers considered too large for initial conserving surgery: results of a phase II study

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Introduction: This study aimed to evaluate the rate of pathological complete response to preoperative chemoradiotherapy and its level of acute toxicity.

Material and Methods: Sixty women were treated (11/2001–11/2003) by preoperative chemoradiotherapy and breast surgery. One patient withdrew her consent during treatment. Median age was 49 years (31–65). Median maximal diameter was 45 mm (21–80). Clinical axillary stages consisted of 54% N0 and 46% N1. Some tumours presented with pathological features of aggressiveness (25% histological grade 3, 27% absence of hormonal receptors, 14% HER2 over-expressed). Chemotherapy consisted of 4 cycles of 5FU 500 mg/m^2 (day 1 – day 5) and Vinorelbine 25 mg/m^2 (day1; day 6). Starting with the second cycle, radiotherapy delivered 50 Gy to the breast and 46 Gy to the internal mammary and supra/infraclavicular lymph nodes. Breast surgery (mastectomy or lumpectomy) and axillary lymph node dissection were then performed. Pathological complete response was defined as less than 5% of residual invasive epithelial cells in the tumour, without any mitosis.

Results: The rate of pathological complete response (pCR) was 27% (16/59). Three factors were associated with pCR: histological grade 3, absence of hormonal receptors and a number of mitoses above 10 per 10 high power fields. Breast-conservation was possible in 69% of patients (41/59). Four patients (7%) had to stop their chemotherapy because of toxicity. No patient had diminished radiotherapy dose because of toxicity. There was no toxic death. Twenty-one patients (36%) experienced a grade 3 toxicity and 13 (22%) a grade 4. The only grade 4 toxicities were haematological (22%) or gastrointestinal (2%).

Conclusion: Chemoradiotherapy showed good efficacy, both in terms of pathological complete response (27%) and in allowing breast conservation (69%) with acceptable tolerance. Long-term follow-up is needed to confirm that these good pathological results bode well in terms of patients' outcome.

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Multicenter phase II trial of neoadjuvant exemestane for postmenopausal patients with hormone-sensitive, operable breast cancer: Saitama Breast Cancer Clinical Study Group (SBCCSG-03)

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Back ground: Randomized trials have shown that neoadjuvant letrozole and anastrozole can reduce tumor volume, allowing breast-conserving surgery (BCS) rather than mastectomy for operable tumors. Type I anti-aromatase agent exemestane (EXE) is also promising, however; its use for neoadjuvant therapy has not been reported.

Purpose: Multicenter phase II trial (SBCCSG-03) was designed to evaluate the efficacy and tolerability of neoadjuvant EXE for postmenopausal patients (pts) with estrogen receptor (ER) and/or progesterone receptor (PR) positive breast cancer.

Patients and Methods: Postmenopausal pts with ER and/or PR positive, stage II to IIIB and 3 cm or larger-sized operable breast cancer were assigned to neoadjuvant EXE (25 mg daily) for 4 months and followed by surgery. The pathological response defined as grade 1b, 2 or 3 was assessed by a central review according to "General Rules for Clinical and Pathological Recording of Breast Cancer 2005" published by The Japanese

Breast Cancer Society. The clinical response defined as complete (CR) or partial (PR) response was assessed by caliper, mammography, or ultrasound. BCS rate and adverse events were also evaluated.

Results: Forty-four pts were enrolled and all of them were eligible. The median age was 60 years (range, 48–68). Stage IIA, IIB, IIIA and IIIB were the disease of 26, 8, 4 and 6 pts, respectively. ER and PR positive tumor was in 32 pts, and ER positive and PR negative tumor was in 12 pts. Of 44 eligible pts, three discontinued 4-months EXE due to hematological disorder (grade 3), dizziness (grade 2) or genital bleeding (grade 1), and underwent surgery. There were a few other adverse events, most of which were grade 1. In 41 pts, CR and PR were found in 0 and 27 pts, respectively; clinical response rate was 66%. Stable disease (SD) and progressive disease (PD) were found in 9 (22%) and 5 (12%), respectively. Three pts underwent chemotherapy because of PD. Eight pts refused surgery due to PR or SD after 4-months EXE, and continued EXE. The pathological response was obtained in 13 (43%) of 30 pts who underwent surgery after 4-months EXE; grade 1b in 9 and grade 2 in 4 pts. BCS was performed in 28 pts (93%).

Conclusions: Neoadjuvant EXE is effective and well tolerated in hormone-sensitive, operable breast cancer in postmenopausal pts.

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Epirubicin plus cyclophosphamide vs. weekly paclitaxel as primary systemic therapy in patients with stage II and III breast cancer: randomized phase II study

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Background: Primary systemic therapy (PST), also known as upfront, induction or neo-adjuvant therapy, is given before the standard loco-regional therapy. Not only may it have an effect on potential micro-metastases, but it also has an effect on tumor growth. Response and survival rates achieved by anthracycline and paclitaxel (P) (q 3 weeks (W)) patients (pts) with metastatic breast cancer (BC) are comparable (ECOG1193). Weekly P is expected to produce higher response rates and lower hematological toxicity than tri-weekly P for PST (MDACC2002). The aim of this study was to evaluate the activity and toxicity of weekly P therapy compared with epirubicin (E) plus cyclophosphamide (C) therapy for stage II and III BC with PST.

Methods: Pts with histologically confirmed BC, stage II or III, performance status 0–2, and absence of prior chemotherapy were randomized to either Arm A (EC: E 75 mg/m^2 and C 600 mg/m^2 every 3 W for 4 cycles) or Arm B (weekly P: P 80 mg/m^2 weekly for 12 W). Pts received PST for 12 W, then underwent surgery. All pts received a cross-over regimen as adjuvant chemotherapy after surgery.

Results: As of Sep 2005, 149 pts have been recruited. One hundred and thirty-two pts (Arm A: n = 67, Arm B: n = 65) were evaluable. The clinicopathological characteristics of pts (age, tumor size, stage, hormone receptor (HR) and HER2 status) were well balanced in the two arms. Overall response rate (OR) was 65.7% in Arm A and 66.2% in Arm B. OR in HER2-positive pts was 66.7% in Arm A and 73.9% in Arm B, but there was no significant difference. OR in HR negative pts were equal in both arms. The incidence of grade 3/4 neutropenia (38.6% vs 2.3%, $p < 0.001$) and leukopenia (33.3% vs 0%, $p < 0.001$) were lower in Arm B than in Arm A, while that of nausea(27.5% vs 8.2%, $p < 0.02$) was higher in Arm A. Vomiting and mucositis were more frequently seen in Arm A than in Arm B, but there was no significant difference. The incidence of neuropathy (6.0% vs 52.8%, $p < 0.001$) was higher in Arm B.

Conclusions: Interim analysis of 132 pts suggested that weekly P was associated with lower toxicity than EC therapy, but more frequently induced neuropathy. OR was similar in both therapies. Therefore, induction of PST by weekly P therapy seems to be promising. We are further investigating the pathological response and accrual is still proceeding.

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The effect of pathological response of multicenter phase II trial of fluorouracil, epirubicin, cyclophosphamide (FEC 100) followed by docetaxel (DOC 75) in primary operable breast cancer (JBCRG01: Japan Breast Cancer Research Group)

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Introduction: Preoperative systemic therapy (PST) has been widely used in the treatment of operable breast cancer. This study was designed to evaluate clinical and pathological response, safety, breast conservation (BCS) rate, survival, and translational research of FEC followed by DOC as PST in patients (pts) with operable breast cancer.

Patients and Methods: Eligible patients had primary operable breast cancer with $T_{1c-3}N_0M_0$, $T_{1-3}N_1M_0$, no prior chemotherapy, age 20–60, ECOG Performance Status 0–1, adequate hematological, renal, hepatic and cardiac function, and written informed consent. Preoperative chemotherapy consisted of 4 cycles of FEC (F: 500 mg/m^2, E: 100 mg/m^2, C: 500 mg/m^2) every 3 weeks followed by 4 cycles of DOC (75 mg/m^2) every 3weeks.

Results: From June 2002 to November 2004, 202 pts were enrolled. The median pts age was 46 (range, 25–60). All patients had ECOG Performance Status of 0. Premenopausal was 73%. Tumor stage: T1/T2/T3 7/73/20%. Node positive was 57%. Hormone status: ER positive; 67%, PgR positive; 51%, ER/PgR both positive was 49%. HER2 (IHC) status: 0/1+/2+/3+/unknown 34/27/18/19/2%. Relative dose intensity was 98% for FEC and 95% for DOC. The overall response rate was 73% [95% confidence interval (CI) 66%-79%], with 23% CR, 51% PR. Addition of DOC improved overall response rate from 60% to 73%. BCS was 83%. FEC-DOC treatment, grade 3–4 hematological toxicity included leucopenia 41%, neutropenia 52%, and febrile neutropenia 20%. Grade 3 non-hematological toxicity included nausea 8%, vomiting 6%, fatigue 2%, neuropathy 1%, and myalgia/arthralgia 1%. There were no reports of grade 4 non-hematological toxicity. For pathologic response 190 pts were evaluated by central review. pCR rate was 23% (43/190) [95% CI 17%-29%]. The higher pCR rate was obtained in ER−/PgR−/HER2(3+) pts than in ER+/PgR+/HER2(0) pts [65%(13/20) vs.13%(4/31)].

Conclusion: This is the first multicenter trial in Japan to study of FEC 100 followed by DOC 75 as primary therapy for early stage breast cancer. This regimen was effective and well tolerated therapy for Japanese patients. The results of pathological response suggest that ER/PgR both negative and HER2 positive are correlated with pathological response. From now on relationship between pathological response and prognosis will be analyzed. Further we will analyze apoptosis-related factors.

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The relationship of positive steroid receptor (SR) status with disease outcome in patients treated with adjuvant cyclophosphamide, methotrexate, and fluorouracil (A-CMF) chemotherapy (CHT) and adjuvant endocrine therapy

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Introduction: There is an opinion that SRs are predictive markers for the response not only to endocrine therapy, but also to chemotherapy, with SR-positive breast cancers being less sensitive to chemotherapy. The purpose of this analysis was to determine the relationship of positive SR status with disease outcome in patients treated with adjuvant chemotherapy and adjuvant endocrine therapy.

Patients and Methods: We evaluated a group of 482 early breast cancer patients, diagnosed from 1986 to 1994, who were treated either with adjuvant A-CMF CHT (N = 172), or adjuvant endocrine therapy [ovarian ablation (OA) by irradiation for premenopausal (N = 139), or tamoxifen (TAM) for postmenopausal women (N = 171)]. All patients were either node negative with grade 3 breast cancers, or had 1–3 positive nodes regardless