PP-5-8 Atlas: An International Megatrial of Tamoxifen Duration

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The worldwide overview by the Early Breast Cancer Trialists' Collaborative Group of randomised trials of adjuvant tamoxifen in women with early breast cancer demonstrated a moderate but highly significant improvement in 10-year survival with tamoxifen. Indirect comparisons of trials assessing different tamoxifen durations suggest that more prolonged treatment confers a greater survival benefit but because of the potential risks of tamoxifen, notably endometrial cancer, a more reliable assessment of the risks and benefits of longer treatment is required. Whilst several trials are ongoing which may clarify whether 5 years is of greater benefit than shorter regimens, there are few trials assessing reliably the efficacy and safety of adjuvant tamoxifen beyond 5 years.

We are therefore organising an international "mega-trial", Atlas ("Adjuvant Tamoxifen: Longer Against Shorter"), which aims to recruit some 20,000 women worldwide and thereby to provide definitive evidence on the optimal duration of tamoxifen treatment. The trial uses a pragmatic design for randomisation, and any woman who has been on tamoxifen for some years for whom there is *uncertainty* about whether to stop or continue tamoxifen is eligible for randomisation between either stopping tamoxifen or continuing for 5 more years. Almost no documentation is requested as the chief analysis will be of all-cause mortality to establish whether the more prolonged treatment improves 10-year survival.

PP-5-9 Impact of Adjuvant Chemotherapy in Conservative Treatment of Breast Cancer T1-2N0M0

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Aim: To evaluate the efficacy of adjuvant chemotherapy (local and distant control) in early breast cancer (BC) pts. T1–2 < 2.5 mmN0 underwent conservative treatment (tumorectomy with axillary dissection followed by breast irradiation). *Methods:* From 1985 to 1995, 383 BC pts underwent breast conservative surgery + irradiation 50 Gy/25 F/5 weeks. 305 pts aged 27–59 were randomized to receive postoperative chemotherapy (CMF-6 cycles), Group I-149 pts versus control, Group II-156 pts. Median f/u 59.7 mos.

Results: Local recurrences (LR) occurred in 10 pts (6.7%) Group I and 15 pts (9.7%) Group II, P > 0.05. 20 pts Gr I (13.4%) and 32 Gr II (20.5%) developed distant metastases. The estimated 5-years disease-free survival (DFS) were 83.2%-Group I and 75%-Group II (P < 0.05). There was no significant differences for overall survival between two groups (88.5% and 83.3% respectively). *Conclusion:* Adjuvant chemotherapy (CMF) moderately improve distant control and DFS in early BC pts T1–2 < 2.5 cm N0, underwent conservative treatment.

PP-5-10 Direct Comparisons of Adjuvant Chemo-Endocrine Therapy in Operable Breast Cancer Stratified by ER and Menopausal Status

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Direct comparison of adjuvant treatments is necessary to compare different kinds of therapy in each subgroup. We conducted a prospective randomized trial stratified by ER and menopausal status comparing adjuvant chemo (CHEM; mitomycin C iv, cyclophosphamide po)-, endocrine (TAM, tamoxifen, for 2 years, in premenopausal patients; after oophorectomy), and chemo-endocrine therapy (CHEM + TAM) in UICC stage I, II, IIIA breast cancer. From 1978 to 1991 (median follow-up: 7.2 years), 1579 patients were evaluated for disease-free (DFS) and overall survival (OS). In premenopausal ER-positive patients, TAM after oophorectomy showed comparative effect on DFS and OS, as CHEM or CHEM + TAM. In postmenopausal ER-positive group, there was a significant higher difference in CHEM + TAM, compared with TAM, or CHEM (p = 0.0519 for DFS, p = 0.0159 for OS). The addition of chemotherapy to TAM appears to be effective in prolonging survival in postmenopausal ER-positive patients.

PP-5-11 High Dose Mitoxantrone and Cyclophosphamide with GM-CSF in First Line Chemotherapy of Breast Cancer

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The aim of intensified dosage PCT in advanced breast cancer is to overcome drug resistance of cancer cells, possibly using drugs which are active on specific tumor cells as well as characterized by an easily controlled toxicity (such as toxicity on blood cells). We report our experience with 30 patients with locally advanced (n = 15) and metastatic (n = 15) breast cancer, treated with intensified increasing dosage of Mitoxantrone (M) and Ciclophosphamide (C) plus growth factor (GM-CSF). Three levels of dosage were adopted: 15 + 1500 mg/mq; 17.5 + 1750 mg/mq; 20 + 2000 mg/mq; in all cases, 5 μg/kg/day was added, from day 4 to day 14. Toxicity on blood cells was assessed through repeated blood cell count on day 1, 3, 7, 10, 12, 14. Blood cell nadir occurred between day 7 and day 10 (WBC 1436 ± 1080 mm^3; Hb 10.6 ± 1.3 g%; PLT 124,000 ± 48,000 mm^3). Treatment was suspended because of severe bone marrow depression only in 7 cases (23%). Non-haematological toxicity was represented only by nausea and vomiting (III–IV grade WHO) in few cases (8%). GM-CSF treatment was associated with mild symptoms such as fever, skin rashes and postural hypotension, usually on first time of administration (first dose effect). In stage III, response was complete in 7 ± 12%, partial in 40 ± 25%; in stage IV, response was complete in 20 ± 20%, partial in 40 ± 25%. Median actuarial survival was at 21 months. Our data suggest that intensified dosage treatment is feasible and more effective than standard treatment; this might be true also when PCT is integrated with surgery or radiotherapy.

PP-5-12 Intensive Chemotherapy Program with Autologous Bone Marrow Transplantation (ABMT) in Non Metastatic Inflammatory Breast Cancer: Mature Results

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We reported a series of 28 consecutive patients with non metastatic unilateral breast cancer treated in the same French Regional Cancer Center by an intensive chemotherapy program. All patients had a biopsy-proven breast cancer staged T4d, Pev 2 or 3, M0. They received first 4 cycles of high dose 5-Fluorouracil, Epirubicin, Cyclophosphamide (FEC-HD; Am. J. Clin. Oncol., 1993; 16:223) every three weeks. Whatever the response, a radical mastectomy was done as bone marrow collected in the same time. One month later, they received a single course of CDDP 40 mg/m^2 X4, VP 16 400 mg/m^2 X4, Cyclo. 1.5 g/m^2 X3. Radiotherapy completed the treatment after recovery. To date, 28 patients achieved the whole program and are fully evaluable with a median follow-up of 40 months (18–85). Median age was 41 (31–49). 30% of febrile neutropenia and 40% grade 3 or 4 mucositis were the most severe events during the induction phase. A 30% rate of complete histologic response was observed. No major or unexpected toxicities occurred after high dose chemotherapy. Recovery seemed to be earlier for the last patients who were rescued by peripheral blood cell progenitors. With a 40 months median follow-up, 10 out of the 28 patients relapsed (6 in the two first years, 4 during the third, none after 3 years). 5 out the 10 are still alived and had responded to further chemotherapy. The DFS and OS at 24 and 36 months are respectively of 74% (55–86) and 88% (70–95), 60% (40–77) and 78% (57–90)%. Despite high toxicity, the program has been completed without toxic death and the results seem to indicate an unusual favorable outcome for this unfavorable disease.

PP-5-13 Radical Radiotherapy and Effects of Tamoxifen in Patients with Histologically Positive Stumps After Breast Preservation Operations

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In our department, breast preservation therapy was performed on 214 patients. Thirty seven of the patients (17.3%) were found to be stump positive postoperative histological examination. In a examination of hormone receptors, 19 of these patients and were ER positive, 13 were ER negative and five were unknown. The breast cancer was premenopausal in 29 patients and postmenopausal in eight. The residual breast was irradiated with 50 Gy in all patients. Tamoxifen was administrated to all six postmenopausal ER positive patients, and the remaining patients were divided into a group

administrated and a group not administrated tamoxifen. The two groups showed no differences in back ground factors. In the observation period of 34 weeks, localized recurrences were not found in the tamoxifen group but appeared in two patients in the untreated group. The premenopausal ER (+) patients were all comedo type and EIC (+). Concomitant use of tamoxifen appears to be useful as postoperative treatment in premenopausal patients undergoing breast preservation therapy.

PP-5-14 FEC-75 Plus G-CSF in Locally Advanced Breast Carcinoma

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Aim. – To assess efficacy and tolerability of chemotherapy (CT) given every 14 days to increase dose-intensity (DI) and reduce time to surgery in patients with T3/T4 and/or N2 breast carcinoma.

CT scheme. – FEC-75 (5-FU 600 mg/m^2, epirubicin 75 mg/m^2, ciclophosphamide 600 mg/m^2) day 1st plus filgrastim 30 mU SC, days 3 to 12. Courses were repeated every 14 d up to 4 courses (c).

Patients. – From April/94 40 patients (p) have been included in 4 hospitals: median age 54 y (32–65); ECOG 0 40 p; post-menopausal 21 p; T1–2 6 p, T3 19 p, T4b 6 p, T4d 6 p; N0 13 p, N1 9 p, N2 15 p; G2 22 p, G3 8 p. Stages IIb 9 p, IIIa 15 p, IIIb 13 p.

Results. – Courses given: 119. Actual dose: 100% in every c. without delay (DI 150%). Non-hematological toxicity: N&V G2 35 c (29%), mucositis G1 6 c, flu-like synd G1 6 c, G2 1 c, alopecia 40 p. No cardiotoxicity (LVEF measured in 18 p). Hematological toxicity: On day 1 of the course, only 1 p had thrombopenia G1. anemia G1 12 p.

Responses (OR) en 22/35 p (63%): RC 5 p, RP 17 p, EE 13. No progressive disease. Surgery already performed in 33 p (mastectomy 25 p, conservative 8 p).

Conclusions. – FEC-75/14d × 3–4c + G-CSF showed high response rate without severe toxicity. Pathologic CR rate remains low. DI was significatively increased and time to surgery reduced. Radical surgical procedures were performed in all patients in our experience.

PP-5-15 Postoperative Adjuvant Randomized Trial Comparing Chemoendocrine Therapy, Chemotherapy and Immunotherapy for Patients with Stage II Breast Cancer

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The effects of using ftorafur (FT) or PSK (an immunotherapy agent) in combination with adjuvant therapy using mitomycin (MMC) + tamoxifen (TAM) were assessed in stage II, ER+ breast cancer patients. In stage II, ER– breast cancer patients the effects of adjuvant therapy using MMC + FT were compared with those using MMC + PSK. On the day of surgery, MMC (13 mg/m^2) was administered. ER+ patients received one of three regimens, starting 2 weeks after surgery: regimen A (30 mg/day of TAM), regimen B (30 mg/day of TAM and 600 mg/day of FT) or regimen C (30 mg/day of TAM and 3 g/day of PSK). ER– patients received either regimen D (600 mg/day of FT) or regimen E (3 g/day of PSK). Of the 540 ER+ patients, 525 were evaluated. The 5-year survival (OS) was higher for patients who received regimen B than for those who received other regimens (P = 0.063). The 5-year relapse-free rate (RFS) was higher for regimen B than for other regimens (P = 0.010). Stratified analysis revealed better results with regimen B in premenopausal patients and patients positive for lymph node metastasis. Of the 376 ER– patients, 364 were evaluated. There was no significant difference in OS or RFS between the D and E regimens.

PP-5-16 A Study of Postoperative Adjuvant Chemotherapy of 5′-DFUR in Breast Cancer Patients (1st Report) — On Compliance and Safety — "The 5′-BC Study Group" (5′-DFUR Adjuvant Chemotherapy for Breast Cancer Study Group)

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Introduction 5′-deoxy-fluorouridine (5′-DFUR), an analogue of 5-fluorouracil synthesized by Cook et al. in 1976, is used orally to treat stomach, colorectal, cervical, bladder, and breast cancers in Japan. To assess the usefulness of postoperative adjuvant 5′-DFUR chemotherapy in breast cancer, we conducted a controlled comparative study at 153 institutions; control groups received only surgical resection. Subjects were of T < 3 cm, N0 or N1a, M0 and Brt + Ax or over after gross curative resection. From June 1990 to December 1992 (2 years and 7 months), 1217 patients were registered in the study. The report rate of cumulative follow up data was 97%.

Methods Patients were randomly assigned to a repetitive or intermittent dosage group. Repetitive dosage: Method Y (5′-DFUR from 2 wks. after operation at 1200 mg/day × 4 wks., discontinuance for 2 wks. followed by 600 mg/day × 20 wks.) and method X (surgery only). Intermittent dosage: Method B (5′-DFUR from 2 wks. after operation at 1200 mg/day × 4 wks., discontinuance for 2 wks., 1200 mg/day × 2 wks. alternated with 2 wks. discontinuance until 28 wks. after operation) and Method A (surgery only).

Results Compliance was favorable: 91.1% of Method Y and 88.0% of Method B patients achieved 80% or more of the drug administration rate (Actual total dose/scheduled total dose) in our protocol. While incidence of adverse reactions was 24.8% (Method Y) and 27.2% (Method B), most adverse reactions were mild (grade 1 or 2) gastrointestinal symptoms, e.g., diarrhea, etc. Although follow-up results continue to be compiled (median observation time, 4.3 years), interim findings are available on request.

PP-5-17 High-Dose Cyclophosphamide (CTX), Mitoxantrone (MXT), and Paclitaxel (Taxol®, TXL) for the Treatment of Metastatic Breast Cancer (MBC) with Blood Cell Support

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A Phase I study using CTX 6 g/m^2, MXT 70 mg/m^2, in combination with TXL at a starting dose of 250 mg/m^2 in dose escalation for the purpose of determining dose limiting toxicity (DLT), maximum tolerated dose, and efficacy of this drug combination in a transplantation setting with pharmacokinetic analysis of TXL is being performed. Patients between the age of 18–55 with MBC not previously treated with cytotoxic drugs for metastatic disease are eligible. So far, 45 patients were enrolled and 31 patients have completed the treatment. The blood cell transplantation and recovery time was delivered completely in an out-patient setting. Recovery for ANC ≥ 0.5/nl was 10–16, median 12 days. Recovery for platelets ≥ 20/nl was 18–20, median 12 days. 15 patients developed neutropenic fever that required IV antibiotics. Up to the 3rd dose level of TXL, few patients have experienced grade II and III toxicity other than, hematotoxicity. In the 4th dose level, 6 patients were treated; 3 of them experienced DLT; therefore, an extended infusion schedule delivering the 400 mg/m^2 TXL over 6 rather than 3 hours is used. This study is ongoing.

PP-5-18 Adjuvant Epirubicin and CMF +/– Hormonotherapy in More than 3 Nodes Positive Breast Cancer Patients: Preliminary Data

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206 patients with early breast cancer were treated with Epirubicin 110 mg/sqm iv d 1 q 3 weeks × 4 cycles followed by CMF (CTX 500 mg/sqm iv d 1–8, MTX 40 mg/sqm iv d 1–8.5-FU 600 mg/sqm i.v. d 1–8 q 4 weeks) × 4 cycles +/– Hormonotherapy: Goserelin depot sc every 28 days × 2 years in premenopausal patients and Tamoxifen 20 mg/os/day × 5 years in postmenopausal patients. Radiotherapy was given after conservative surgery.

Median age was 42 years in premenopausal patients and 59 in postmenopausal patients.