68 PUBLICATION

COMBINED THERAPY IN THE TREATMENT OF INFLAMMATORY BREAST CANCER

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Inflammatory Breast Cancer (IBC) occurs with an incidence of 1 to 4% among all breast cancer. The prognosis is poor: most women experience metastatic dissemination in the first two years. Patients with IBC are treated at our Institute with Chemotherapy (FEC regimen: 5-FU 500 mg/sqm iv d1, Farmorubicin 100 mg/sqm iv d 1, CTX 500 mg/sqm iv d1 every 3 weeks) × 4 cycles + Lonidamine 450 mg by mouth a day. After 4 cycles of Chemotherapy, responsive patients (CR + PR) are operated on radical mastectomy followed by a further 4 cycles of FEC + Lonidamine and Radiotherapy. Stable (NC) and Progressive patients are treated with Radiotherapy and Salvage Chemotherapy (Mitomycin 15 mg/sqm iv dl every 6 weeks + Mitoxantrone 10 mg/sqm iv dl every 3 weeks × 6 cycles). Twenty-seven patients entered in the study. We obtained complete remission + partial remissions in 22 patients (81%), a minimal response in 3 patients, NC in 2 patients. Three patients with minimal response were operated on radical mastectomy after Radiotherapy.

69 PUBLICATION

INTENSIFIED ADJUVANT CHEMOTHERAPY FOR PATIENTS WITH BREAST CANCER AND >10 POSITIVE LYMPH NODES. A PHASE II STUDY

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Patients (pts) with breast cancer and >10 positive axillary nodes have a poor prognosis. Between 3–92 and 11–94, 41 such pts were treated with intensified adjuvant chemotherapy, consisting of 6 cycles of epirubicin (E) (110 mg/m^2) every 2 weeks with G-CSF support. Thirty-six pts underwent modified radical mastectomy and 5 partial mastectomy. Postoperative RT was administered in 3, and hormonotherapy in 8 pts. The median age of the group was 58 (range, 32–68) years. Twenty-two pts had ER$^+$, 11 ER$^-$ and 8 unknown. Thirty-seven pts (92%) received 6 cycles of E. Median dose intensity of E was 54 mg/m^2/week. After a median follow-up of 14 (range, 3–35) months, 17 (42%) have released and 11 (27%) died. Site of relapse was local (2 pts), bone (2), soft tissue (4) and viscera (12). Grade 3 toxicity included vomiting (10%), anemia (2%), alopecia (66%) and stomatitis (2%). We conclude that this intensified treatment is feasible and well tolerated.

70 PUBLICATION

CMF OR CMF + RT AS ADJUVANT THERAPY IN PATIENTS WITH STAGE I–IIIA BREAST CARCINOMA

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This study is a retrospective and nonrandomized study. Two hundred and twenty nine patients with operable stage I–III A breast carcinoma were included in this study. Median age of the patients was 42 (range: 24–71). All of the patients received adjuvant therapy (CMF (group 1): 89 patients, CMF + RT (group 2): 140 patients) after radical or modified radical mastectomy because of the axillary lymph node involvement, T3 tumor, or lymphovascular or stromal invasion. They were followed up between October 1981 and December 1993. CMF chemotherapy protocol was begun 2 or 3 weeks after surgery, and applied for six cycles with 4 weeks intervals. In the CMF + RT arm, radiotherapy was applied after 2 or 3 cycles of chemotherapy, to the chest wall and axillary lymph nodes region. Dose of RT was 4500–5500 cGy. Mean DFS period was 97 months (1.4–152.8+ m) in group land 55 months (2.6–110 m) in group 2. Mean OS time was 120 m (13–152 + m) in group 1 and 105 m (9.9–142 + m) in group 2. The effects of different prognostic factors on DFS and OS were analysed. In univariate analyses by the Kaplan-Meier life-table method, only the number of positive axillary lymph nodes was found statistically significant on DFS and OS. In multivariate analyses by the step-wise cox-regression model, tumor size and the number of positive axillary lymph nodes were found statistically significant on DFS, and the number of positive axillary lymph nodes was found statistically significant on OS. There was no difference between the groups according to the local relapse and distant metastases. Nausea-vomiting, leukopenia and alopecia were the major side effects of these therapies.

71 PUBLICATION

COST OF DRUG TREATMENT FOR BREAST CANCER IN UKRAINE

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Two protocols are classically utilized in chemotherapy of breast cancer (CMF and FAC) such as Tamoxifen (T) is utilized in hormonal therapy. In Ukraine the minimal available cost of these regimens (per 1 patient with height 165 cm and weight 65 kg-S = 1.7 m^2; US dollars) are $269 (6 cycles of CMF on Bonadonna with C po) or $377 (6 cycles of CMF on Bonadonna with C iv). $693 (6 cycles of FAC on Buzdar) and $146 (20 mg of T every day, total-2 years). We have assessed need of adjuvant therapy in our region: CMF-30%, FAC-10% and T-50%; and accordingly for metastatic breast cancer: FAC-50%, CMF-25%, T-75%. Thus total cost of the antineoplastic drug therapy of one hundred patients in Ukraine is $22,301 (stage I–III) or $58,092 (metastatic disease). In 1994 504 women with breast cancer in clinical stages I–III and 314 women with metastatic breast cancer (including 64 primary patients with dissemination) were diagnosed in Lviv region. We had needed $294,805 for their drug therapy. It is three fold higher than annual budget of our region for total drug therapy of the patients with malignant diseases. Unfortunately new effective (but very expensive) methods of breast cancer therapy—e.g. LHRF (Zoladex), Taxol, rhCSF (Neupogen, Granocyte) etc.—are impossible in Ukraine today.

72 PUBLICATION

MECHANISTIC STUDIES OF TAMOXIFEN HEPATOCARCINOGENESIS: PEROXISOMAL PROLIFERATION

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The antiestrogenic drug tamoxifen (TAM) is a strong liver carcinogen in the rat. As peroxisome proliferators induce liver cancer probably by an epigenetic mechanism the effect of TAM on peroxisomes, peroxisomal enzymes and peroxisome proliferator inducible CYP4A1 activity was studied in the rat. Comparisons were made with the new noncarcinogenic antiestrogen, toremifene (TOR), and with clofibrate (CLO). TAM, TOR (0.10 mmol/kg) or CLO (0.10 or 1.03 mmol/kg) were administered daily to female SD-rats p.o. for 14 days. Morphometric analysis of hepatocytes was performed. Peroxisomal β-oxidation (β-OX) activity and hepatic CYP4A1-dependent lauric acid 12-hydroxylase (LAH) and catalase activities were measured. The volume density (VD) of peroxisomes increased 2.4-fold in the high-dose CLO rats. In the TAM rats the VD of peroxisomes or mitochondria increased 1.8- or 1.3-fold, respectively. In the TOR rats the VD of mitochondria increased 1.4-fold. Either TAM or TOR had no effect on peroxisomal β-OX or on microsomal LAH activities. The high-dose CLO increased the β-OX rate 3.4-fold and LAH activity over 10-fold ($P < 0.001$). Low-dose CLO had no effect on these activities. The antiestrogens had only minor effects on catalase activity. In conclusion, the slight peroxisome proliferating effect of TAM with no concomitant increase in enzyme activities does not explain its carcinogenic action. This agrees well with the recent findings that a genotoxic product of TAM metabolism is probably involved in the cancer induction process.

73 PUBLICATION

POST-OPERATIVE RADIOTHERAPY AND CONCOMITANT ADJUVANT CHEMOTHERAPY FOR BREAST CARCINOMA

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Between May 1992 and December 1993, 72 patients operated for breast carcinoma underwent radiotherapy (RT) and concomitant adjuvant chemotherapy (CT). There were 2 T0, 23 T1, 47 T2 and 1 T4b. Lymph node status was 59 N0, 10 N1 and 4 unknown.

Surgical treatment was lumpectomy (59) or mastectomy (13) and axillary dissection for all. Radiation therapy delivered 50 Gy in 5 weeks to the breast or chest wall. A 10 Gy boost was added to the tumor site after lympectomy. The internal mammary chain was irradiated in 64 patients, the subclavicular area in 53 and the axilla in 1 patient. The CT regimen was a combination of Mitoxantrone (12 mg/m^2), 5-FU (500 mg/m^2) and Cyclophosphamide (500 mg/m^2), 6 cycles were delivered with 21 days interval. Compliance to RT evaluated on dose and treatment length was good for 88%. On the 65 patients analysed for CT: 98% received

all 6 cycles at the prescribed dose, but 69% strictly respected intercycle intervals.

Mild digestive and cutaneous toxicity (grade 1 and 2) was observed in 50%. Major toxicity was neutropenia (grade 2 or 3) in 18 patients and 1 severe infection. The 3 year actuarial survival rate was 87%. No local relapse was observed. Metastases occurred in 6 patients.

These preliminary results show that this concomitant association is safe although compliance to chemotherapy should be improved.

74 PUBLICATION

CONCOMITANT ADJUVANT CHEMOTHERAPY (FNC REGIMEN) AND RADIOTHERAPY IN OPERABLE STAGE II BREAST CANCER (O.B.C.)

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The purpose of multimodality treatment including simultaneous radiochemotherapy is to reduce the total length of the adjuvant treatment after surgery. Aims of study were to evaluate the compliance, global toxicity and local cutaneous side effect. The treatment scheme is F.N.C (F: Flourouracil 500 mg/m^2, N: Mitoxantrone 12 mg/m^2, C: Cyclophosphamide: 500 mg/m^2) every 21 days. Six cycles for N+, 4 cycles for N− with poor prognosis (RH- or SBR III). Radiotherpy is indicated by the consensus of the "Societe Française de Radiotherapie Oncologique" S.F.R.O. (50 Gy/25 fractions/5 weeks, 15 Gy overdose when T > 10 mm).

We report a feasibility study in 154 pts with O.B.C. included from May 90 to October 95 Median age: 49, 5 y (29–72), postmenopausal: 46.8%; premenopausal: 52.6%; Performance Status O: 96.7%, 1: 2%, unknown: 1.3%, Radical surgery: 29.9% conservative: 69.5%, N−: 29.9%; N+: 70.1%. Ductal carcinoma: 85.7%, lobular: 5.8%, SBR I: 2.6%, SBR II: 26.6%, SBR III: 65.6%.

Total number of courses was 773 (60.4% of pts received 6 courses). Full dose of N was administered to 84.4% of pts, F to 90.3%, C to 88.3%. Interval between 2 cycles was 21 days in 30.9% pts, 28 days in 45.4% pts, upper than 28 days in 23.7% pts. Median total radiotherapy dose was 50 Gy. Main toxicities observed (per pts) were: gastrointestinal grade 3–4: 4.6%, dysphagia: 27.9%, leucopenia grade 3–4: 12.3%, anemia grade 2: 2%, thrombocytopenia grade 2: 1 pt. A reversible cardiotoxicity occurred in 15 pts including extrasystole: 1 pts, low blood pressure: 2 pts, pericarditis 3 pts. Local toxicity was mild (grade ⩽ 1: 62.3%, grade 2: 16.9% and grade 3: 4.5%). No major pulmonary toxicity was observed. Quality of life (E.C.O.G scale) was performed to evaluate the repercussion of this treatment grade 0: 44.2%, grade 1: 34.4%, grade 2: 7.8% and grade 3 in 1 pt. Well acceptability of treatment in 51.9% of pts.

Mitoxantrone containing chemotherapy and postoperative radiotherapy can thus be combined in an adjuvant treatment program with good compliance and acceptable toxicity. Ongoing or further study of a large patients groups comparing various strategies of chemotherapy and radiation sequencing will be needed to confirm our data.

75 PUBLICATION

A PILOT STUDY OF ADJUVANT POSTOPERATIVE CHEMOHORMONAL THERAPY WITH 5-FLUOROURACIL, DOXORUBICIN, CYCLOPHOSPHAMIDE, VINDESINE AND TAMOXIFEN FOR RESECTABLE BREAST CANCER

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Adjuvant systemic therapies have proved effective to increase disease-free survival (DFS) and total survival at 5 and 10 years in patients with "resectable" breast cancer. However, the amount of the benefit is at best moderate. There is a need of more effective regimens.

We show the results of a pilot trial of postoperative adjuvant therapy with 6 cycles of 5-Fluorouracil 600 mg/m^2, doxorubicin 50 mg/m^2, cyclophosphamide 600 mg/m^2 and vindesine 3 mg/m^2 (maximum 5 mg), all endovenous on day 1, repeated every 28 days, plus Tamoxifen (20 mg/day) continued for 2 years (not in ER negative tumors). This schedule of chemohormonotherapy had been demonstrated highly active in metastatic breast cancer. Three-hundred and five patients (pts) have been treated. Menopausal status was: premenopausal in 93 pts and postmenopausal in 212. ER status was (+) in 90 pts, (−) in 61 pts and unknown in 154 pts. Twenty-three pts had node negative stage II tumors with peripheral blood or lymph vessel invasion (PBLI), 75 pts had 1 to 3 positive nodes, 33 pts had 4 to 10 positive nodes, 15 pts had 10 or more positive nodes and 159 pts had technically respectable stage III tumors +/− axillary nodes (N0, N1 o N2). (stage IIIA 87 pts and stage IIIB 72 pts). More than 90% of the patients received 6 cycles of chemotherapy at full dose. Median follow-up is now 44 months (80 pts followed for 5 years or longer). Actuarial 5 year DFS is 84% for N(−) stage II with PBLI; 79% for pts with stage II (1–3 nodes); 70% for pts stage II (3–10 nodes); 62% for stage II (>10 nodes) and 56% for stage III. DFS and total survival according to menopausal status and ER status will be presented.

We feel that such stimulating results in this uncontrolled pilot trial deserve testing in a randomized multi-institutional study.

76 PUBLICATION

ADJUVANT FOUR CYCLES OF EPIRUBICIN AND CYCLOPHOSPHAMIDE WITH RADIATION THERAPY IN OPERATED STAGE II–III BREAST CANCER

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Between April 1992 and March 1993, 96 operated patients with stage II–III breast cancer received adjuvant treatment consisting of Epirubicin (70 mg/sqm) and Cyclophosphamide (600 mg/sqm) I.V. every three weeks for 4 cycles and followed by locoregional radiation therapy. Median age was 41 (range 25–60). Sixty-eight patients were in stage II, 28 in stage III. Seventy-nine we premenopausal and 17 postmenopausal. WHO Grade 2–3 side effects were: Leucopenia 18%, and alopecia 60%. Cardioxicity was not observed.

After a median follow-up of 28 months, 18 patients presented recurrences (3 local and 15 distant) five patients died during the follow-up. Adjuvant combined 4 cycles of EC followed by radiation therapy is an affective treatment with high local and distant control, and shortens the treatment time in stage II–III operated breast cancer.

Small cell lung cancer

77 ORAL

RANDOMISED COMPARISON OF ALTERNATING OR SEQUENTIAL SCHEDULES OF CHEMORADIOTHERAPY IN LIMITED SMALL CELL LUNG CANCER (SCLC) TRIAL OF THE EORTC LCCG(08877)

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Combined modality therapy is becoming standard treatment for "good prognosis" patients with SCLC but the optimal schedule and timing of thoracic irradiation is as yet unclear.

The EORTC LCCG has completed a randomised comparison of alternating (A) vs sequential (S) schedules of CDE chemotherapy and thoracic irradiation (50 Gy in 20 fractions) with identical total chemotherapy and radiation doses and overall treatment time; the schedule as the only variable. This trial will close on 31.3.1995. Three hundred and forty-nine patients have been randomised (174 in A, 175 in S), 11 were inelligible. Mean age was 60, M/F = 2/1, PS 0 (46%), 1 (47%), 2 (5%) and 3 (2%). Weight loss was < 10% in 76%. All these parameters are similar in both arms. First full analysis will be performed 6 months following trial closure and will be presented. Interim analysis performed on 285 patients (144 A and 141 S) showed consistently higher rates of