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