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RESULTS OF ADJUVANT and NEO-ADJUVANT CHEMOTHERAPY in INCIPIENT STAGES of BREAST CANCER.

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Since 1978 it was administrated adjuvant chemotherapy (ChT), 6-10 monthly cycles, to 245 patients (first group) with breast cancer in incipient stages (I, II and IIIa) at whom axillary lymph nodes metastasis was histopathologically found (N+). At most of these patients radiotherapy (RT) was applied too. The results obtained were better - regarding the rate of complete remission (free disease) and its duration, the rate and precocity of the appearance of the metastasis and the length of survival - than at the 280 patients (historical control group) operated and treated only with RT for the N+.

But even in that first group the results were unsatisfactory: over 50% of the patients developed metastases in the first 3 - 5 years after mastectomy, still the survival period being rather bad and short.

Because in most cases the disease had already been micro-disseminated at the moment of the diagnosis, for 12 years it was applied at 118 patients in the same stages (second group) neo-adjuvant ChT, consisting of 2-4 monthly cycles, plus RT at 65% of the cases and ChT after radical mastectomy, up to 6-10 cycles altogether. The preoperative ChT and RT induced the sterilization of the tumor and/or of the axillary lymph nodes with over 50% of the cases. Hence, at these cases with better histoprognosis, the therapeutical results in the second group were actually far better regarding the same parameters above mentioned, tested at 3, 5 or 10 years of survival.

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EFFECT OF THYMIC EXTRACT "TFX-THYMOMODULIN" ON T LYMPHOCYTE SUBSETS DURING POSTOPERATIVE RADIOTHERAPY FOR BREAST CANCER.

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A quantitative analysis of peripheral T lymphocyte subsets was performed to evaluate the effectiveness of TFX-thymomodulin, a bovine thymic extract in raducing the immunosuppressive effect of postoperative radiotehrapy in breast cancer patients.

Twenty women with histologicaly proved breast cancer, assigned to stage II using the criteria of TNM classification, were randomly divided into two comperative groups: the first one was treated with radiotherapy only, and the second one was treated with thymic extract, TXF-thymomodulin, besides radiotherapy. In both groups the initial CD4+/CD8+ ratio was lower than the normal range, which was mainly cused by a decrease in T helper subset. After tretment, the increase of CD4+/CD8+ ratio was significant ($p < 0,01$) only in the group, treated with radioimmunotherapy. We found significantly lower reduction of CD4+ and HLA-DR+ cells ($p < 0,05$) in breast cancer patients group treated with radioimmunotherapy, compared to group treated with radiotherapy only.

In conclusion, TFX-thymomodulin seems to be effective in reducing side, immunosuppressive effect of postoperative radiotherapy for breast cancer.

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EFFECTIVE REMOVAL OF BREAST CANCER CELLS FROM BONE MARROW

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High dose chemotherapy with autologous bone marrow transplantation (ABMT) has shown promise in the treatment of breast cancer. There is, however, a risk of transfusing tumor cells with the BM cells. To eliminate breast cancer cells from normal human BM, monoclonal antibodies (MAbs) reactive with breast cancer were used with immunomagnetic beads or as immunotoxins (ITs) in model experiments. With 2 cycles of immunomagnetic elimination the individual MAbs removed 2.7- >6.0 log of T47D and MCF7 tumor cells from a single cell suspension, as assessed in a reproducible soft agar assay. Different combinations of 2 antibodies were only marginally more effective than the individual MAbs, whereas 5-6 log removal was obtained with a combination of 3 antibodies. Three ITs involving MAbs and Pseudomonas exotoxin A were highly active. Thus, more than 5 log removal was obtained with individual ITs at a concentration of 1.0 μg/ml, and with a mixture of all three ITs, each at a concentration of 0.1 μg/ml. The methods were equally effective when the tumor cells were mixed with BM cells at a ratio of 1:10. Neither of the procedures significantly affected the survival of normal progenitor cells, assessed in CFU-GM and CFU-GEMM assays. The results indicate that both methods can be used safely and effectively to eliminate tumor cells from the bone marrow in conjunction with ABMT in patients with breast cancer.

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NEOADJUVANT CHEMOTHERAPY OF INFLAMMATORY BREAST CANCER WITH CYCLOPHOSPHAMIDE,ADRIAMYCINE AND PLATINUM (CAP).

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Preoperative chemotherapy is a logical approach in IBC,since surgery and radiation failed to cure this life threatening disease.The aim of our study was to evaluate preoperative chemotherapy(3-4 cycles) and consecutive surgery with post-operative 3 cycles of chemotherapy.So far, 73 pts with IBC entered the study,68 being evaluable for chemotherapy treatment (2 cycles) and 37 underwent to surgery and completed the whole programme.The chemotherapy consisted Cyclophosphamide 2oo mg/m² day 1,3,5.Adriamycin 5o mg/m² day 1 and Platinum 3o mg/m² day 1,3 and 5. Evaluating preoperative chemotherapy, CR was registered in 48 pts with cutaneous lymphangiosis (71%), PR in 14, with response of 91% (62/68).Primary tumor regressed in 62 pts (16 CR, 44 PR 81%) and axillary nodes responded in 36/52 pts (CR 1o, PR 26-69%).Thirty seven pts underwent mastectomy with lymphnode disection.Five pathologic remissions were found, and in 3 cases microscopic disease was registered. The recurrence free period ranged 2-41 months (M=14+mos), and survival from 7-55 mos (M=23+mos).Twelve pts are still disease free, 2-49+mos after start of treatment.These data showed that IBC might be cured by applied treatment.

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PREDICTION OF BREAST CARCINOMA RESPONSE TO PREOPERATIVE CHEMOTHERAPY.

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Early effects of AVCMF or FEC preoperative chemotherapy (CT) were evaluated by Computer Cell Image Analysis (SAMBA) on sequential cytopunctures in 64 primary operable breast carcinoma (T2-T3). 27 carcinomas had shown objective regression and 37 no regression after 3 cycles of CT.

Low-cytologic grading ($P<0.01$), low S-phase ($P<0.001$) and small nuclei ($P<0.05$) before treatment were significantly related to no regression. Comparing Samba DNA histograms before treatment and after the 1rst cycle in 54 tumors, tumors were divided in 3 groups ; in group 1 (27), no changes were noted after the 1rst cycle; in group 2 (17), some changes were observed with an increased G2M; in group 3 (10), all showed obvious changes in DNA profiles with additionnal values in (G2+M)x2 and (G2+M)x4. In groups 1 and 2, 2/27 and 9/17 showed objective regression. In group 3, all had objective regression ($P<0.0001$), including 5 histologic CR.

To predict if a tumor will belong to the sensitive (R+) or to the resistant (R0) group, we applied a stepwise linear discrimant analysis to the 15 Samba parameters studied for 25 tumors previously classified in 2 groups (R+ and R0). Before treatment, 2 parameters permitted 84% of well-classified tumors and after the 1rst cycle 9 parameters permitted 88% well-classified tumors. A test set of 10 other tumors showed that those percentages allow a good prediction in 80% of cases both before CT and after the 1rst cycle. Finally,on 9 new cases, using discriminant functions calculated from the training group, a good prediction was obtained in 89% before CT.

From our results, it seems possible to select, before treatment non-responsive tumors with low-grade, small nuclei and low-S phase, for which treatment would be surgery first. If results of our Image Analysis tumor classification are confirmed on a larger group, it should be helpful for a better selection of patients.

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A RANDOMISED TRIAL OF ADJUVANT VERSUS NEOADJUVANT ENDOCRINE CHEMOTHERAPY OF OPERABLE BREAST CANCER

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We have now undertaken a randomised feasiblity trial comparing adjuvant with neo adjuvant chemotherapy combined with tamoxifen for treatment of primary breast cancer.

This trial has recruited over 200 women with newly diagnosed stage 1 or 2 breast cancer confirmed on fine needle aspiration cytology presenting at the Royal Marsden Hospital. Originally we were using mitomycin C, mitozantrone and methotrexate but because of a drug interaction we have now changed this to mitozantrone 10 mg/m² with methotrexate 30 mgs/m² combined with tamoxifen 20 mgs/day (2MT). The chemotherapy is given for 8 cycles and the tamoxifen continues for 5 years. Patients have been randomised to primary surgery before 2MT (adjuvant arm) or after 4 courses of chemotherapy (neoadjuvant arm) with a further 4 courses given after surgery and radiotherapy. The objective response in the neoadjuvant arm is over 85% with a significant reduction in requirements for mastectomy ($p<0.01$). We have compared these responses with mammographic ultrasound and pathological changes. We are also undertaking needle aspiration for cytology for biological markers within this programme and will be monitoring for local relapse and mortality.