85 P

MODULATION OF DECREASED ADHESION MOLECULE EXPRESSION ON BREAST CANCER CELL LINES IN VITRO

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Adhesion molecules are membrane proteins responsible for cell adhesion and cellular recognition. In order to further our knowledge about the role of adhesion molecules (AM) in the context of breast cancer, the following experiments were designed.
By using cell lines ZR-75-1, MCF-7, SK-BR-3, and HBL-100, the expression of AMS, ICAM-1, V-CAM, VLA-4, LFA-1alpha, LFA-1beta, LFA-3, beta-1-integrin and beta-3-integrin using monoclonal antibodies was analyzed. Cytokines Interleukin-2 and -6, Interferons alpha and gamma, Tumor Necrosis Factor-alpha (TNF) and Granulocyte/Macrophage-Colony Stimulating Factor (GM-CSF) were tested for the ability to induce adhesion molecules.
ICAM-1 and VLA-4 were expressed in a significantly lower degree by malignant breast cancer cell lines, as compared to the benign cell line HBL-100. A discordant picture was found concerning the ability of various cytokines to further increase the expression of adhesion molecules: Thus, TNF alpha increased the expression of ICAM-1 in a dose dependent manner on the HBL-100, the SKBR-3 and the ZR-75-1 cell lines, albeit to a different degree. GM-CSF was able to induce ICAM-1 expression in the SKBR-3 cell line only, whereas interleukin-2 induced the expression of ICAM-1 on the MCF-7 cell line.
Concerning the expression of ICAM-1 on tumor cells, induced by TNF, lymphokine-activated killer cells result in lysis of target-cells in the presence of monoclonal anti-ICAM-1 antibody. This did not occure in the tumor cells that express ICAM-1 in a much lower degree. However, the defect to express adhesion molecules may constitute a reason for the metastatic potential and the spread of malignant tissue in vivo and the defective recognition and subsequent destruction of tumor cells by the immune system.

86 P

USEFULNESS OF COLOR DOPPLER IN ASSESSING BREAST INTRACYSTIC OR INTRADUCTAL SOLID LESIONS

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The visualization of solid, echogenic content within a cystic lesion or a dilated duct poses the diagnostic problem of differentiating debris and clots versus a solid disorder. We used Color Doppler (CD) to asses vascular abnormalities within intracystic and intraductal lesions.
Between January and November 1995 we encountered 48 complex cystic lesions and 9 dilated ducts with echogenic material. We used high frequency US probes (10 or 13 MHz) to assess the lesions and we also performed CD with low PRF (500Hz) to detect slow flow.
All the patients underwent US guided aspiration biopsy of the complex cistic lesion with the tip of the needle carefully directed within the echogenic portion. In 39 cases the CD was negative as well as the cytological exam. Nine CD-positive cases were associated with 7 papillomas and 2 carcinomas and underwent surgery. Blood flow signal had been detected in 3 of the 4 cases with papilloma, while one was falsely negative. Two small cystic lesions (diameter less than 7mm) showed a clear CD signal, due to an artefactual intralesion projection of a nerby running vessel: the cytology was negative.
We think that CD should always be performed in the assesment of intracystic and intraductal solid projections, but a better sensitivity to flow in small blood vessels is still needed.

87 P

BIOLOGICAL INDICATIONS TO SURGICAL TREATMENT FOR EARLY BREAST CANCER.

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The research of new biological indicators for tumor malignity is an important tool to improve the prognostic and optimize therapeutical options.This work wants to evaluate clinical power of Flow Cytometric Analysis in order to identify new prognostic stages and modify the choiche of treatment in breast cancer.
From a series of 100 breast cancer in two years we have determinated FCA (ploidia, SPF and G2/M), pTNM and Hormonal Receptors, identifying a group of patients with optimal characteristics (T1, DI=1, SPF < 7%) for minimal surgery (no evidence in this group of limphonodal metastasis).
According to our data, the diploid breast cancer with T<2 cm and SPF<7% are "true early" breast cancer with a high title of HR, a high number of patients in menopausal status and without limphonodal metastatis.
Treatment for postmenopausal patients with these characteristics, could be lumpectomy in local anesthesia and Tamoxifen for 2 years (20 mg/die) without axillary dissection. This procedure is saving for cost, morbidity and psycological trauma for the patients and can be justified by the consideration that limphonodal dissection is important only for prognosis and can be usefully sudstituted by FCA.

88 P

CARBOPLATIN, ETOPOSIDE PLUS UFT MODULATED BY ORALLY LEUCOVORIN LOW DOSE SCHEDULE (FLEC) IN METASTATIC BREAST CANCER (MBC).

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Based on our previous experience with Carboplatin – Etoposide, a modulation with UFT (Tegafur and Uracil) and low-dose of Leucovorin was added trying to increase the number and duration of response in MBC patients (pts).
PATIENTS AND METHODS: Twenty-three pts with previously untreated MBC received at least 3 cycles of FLEC: Carboplatin 100mg/m²/IV, days 1-3, Etoposide 100mg/m²/IV, days 1-3; UFT 10mg/kg/d and Leucovorin 30mg/8h/d both orally, days 7-21. Mean age was 54 (35-74) years; ER+, 11 pts, PR+, 7 pts. Dominant metastasis sites were viscera, 16 pts; bone, 4; soft tissues, 3.
RESULTS: Cycles mean number was 5 (3-6). Ten pts (43%) obtained partial response, 1 patient with lymphatic metastasic disease had complete response (overall response rate 48%, 95% c.i. 28 to 68%). Response rate according to the predominant site of disease was: soft tissues 1/4 (25%), bone 0/3 (0%), visceral 9/16 (56%). Response median duration was 7,25 months (range 3-,15+); median survival, 15.5 months (range 7-,20+). Levels of CEA and CA 15.3 serum markers correlated well with clinical responses to FLEC (CEA 73 % and CA 15.3 80 %). Toxicity consisted of moderate myelosuppression (grade III granulocytopenia, 5 pts, anemia grade III, 4 pts, thrombocytopenia grade III, 2 pts), and diarrhoea grade III, 3 pts. Dosification of UFT and Leucovorin was reduced in 8 pts (digestive intolerance). There were no treatment-related deaths.
CONCLUSION: The FLEC scheme is active in metastatic breast cancer and merits further evaluation and comparison with other chemotherapy schedules.

89 O

EFFECT OF PREVIOUS ADJUVANT CHEMOTHERAPY ON THE ACTIVITY AND EFFICACY OF CEF REGIMEN IN METASTATIC BREAST CANCER PATIENTS.

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The effect of previous adjuvant chemotherapy (ACT) with or without anthracyclines on response rate (RR), progression free survival (PFS) and overall survival (OS) was evaluated in 326 metastatic breast cancer patients treated with CEF (Cyclophosphamide, Epidoxorubicin, Fluorouracil)-based regimens, as first line chemotherapy. One hundred forty-four patients (44%) did not receive ACT, 143 (44%) received CMF-based ACT and 39 (12%) anthracycline-based ACT. Univariate analysis showed a lower probability of response in patients previously treated with ACT (RR=43%) than in patients who did not (RR=58%; p=.02). No difference between CMF-based and anthracycline-based ACT was observed. A longer OS was observed in patients who did not receive ACT (21.1 months) compared to patients previously treated with CMF-based (15.3 months) or anthracycline-based (15.8 months) ACT. Multivariate analysis confirmed ACT as an indipendent prognostic factor associated with a poor RR, PFS and OS.
Previous ACT adversely affects the activity and efficacy of CEF, when used as first line regimen in metastatic breast cancer patients. No difference between CMF-based and anthracycline-based ACT was observed. Because of the poorer activity and efficacy observed, patients who relapse after ACT should be considered for treatment with new drugs or new strategies.

90 P

ASSOCIATION OF LACTOSAMINE TYPE 2 OLIGOSACCHARIDE STRUCTURES WITH MUC-1 APOMUCIN IN THE HUMAN BREAST CANCER CELL LINE SKBR5

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Tumor-associated mucins are high molecular weight glycopeptides involved in the cytoadhesive properties of cancer cells. The proadhesive action of mucins seems to rely on the high degree of glycolisation, in particular on the high content of lactosamine type 2 carbohydrate structures of the Lewis (Le) family. In order to characterize the carbohydrate profile of tumor-associated mucins, we determined the expression of Le carbohydrate antigens on soluble tumor mucins secreted by the LeY^+ human breast cancer cell line SKBR5. After purification of mucins by gel permeation chromatography followed by immunoprecipitation with the anti LeY mAb ABL 364, the obtained LeY-carrying mucin was tested for the reactivity with a panel of carbohydrate-specific mAb's. As determined in a crossed determination ELISA system, the LeY-carrying mucin showed a strong reactivity with mAb's directed against the lactosamine type 2 epitopes LeX and sialyl-LeX (sLeX). We also determined the reactivity of the LeY-carrying mucin with mAb SM-3 directed against the protein core of MUC-1, an apomucin synthesized by various breast cell lines in vitro. In crossed immunodetermination ELISA there was only a weak binding of mAb SM-3 to the LeY reactive material. However, the binding reactivity increased significantly when the material was pretreated with neuraminase. In conclusion, our data demonstrate that in SKBR5 mucins (a) the LeY oligosaccharide structure is associated with the MUC-1 apomucin and (b) beside LeY, in SKBR5 cells the MUC-1 apomucin additionally bears the lactosamine type 2 oligosaccharide structures LeX and sLeX. Since the detection of the MUC-1 core protein by mAb SM-3 requires the pretreatment of the soluble material with neuraminase, our findings also suggest that the content of sialic acid plays an important role in determining the antigenetic profile of LeY-reactive mucins synthesized by SKBR5 breast cancer cells.