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TGF-b REDUCES NITRIC OXIDE PRODUCTION BT TUMOUR ASSOCIATED MACROPHAGES

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Previous studies have shown that the polyamine producing enzyme arginase, is increased in the serum of breast cancer patients. Tumour derived TGF-b has been found to inhibit nitric oxide production from macrophages in a methylcholanthrene induced tumour model. We hypothesised that TGF-b regulated arginine metabolism in the hypoxic environment of breast tumours. To determine the pathway of arginine utililisation within tumours we measured nitric oxide production from both tumour associated macrophages and monocyte derived macrophages (MDMs), cultured in hypoxic conditions with TGF-b.
Results: TGF-b levels were significantly increased in the serum of malignant compared to benign breast cancer patients (101.17 ±14.9 vs 52.07±15.6 ng/ml p=.018). Tumour associated macrophages (TAMs) produce lower amounts of nitric oxide than normal tissue macrophages (2±3 vs 6.4 ±3 pM/well/ug protein). MDMs cultured under hypoxic conditions in the presence of TGF-b produce less nitric oxide than those cultured with hypoxia alone (10 ±2 vs 30 ±7 pM/well/ug protein).
Conclusions: Taken together with evidence of increased arginase in these patients, this data indicates that arginine within breast tumours is diverted from the nitric oxide pathway, possibly to the polyamine producing arginase pathway. In this way increased arginase activity may promote tumour growth by providing polyamine substrates.

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EPIRUBICIN INTERMEDIATE DOSE PLUS CYCLOPHOSPHAMIDE IN THE TREATMENT OF METASTATIC BREAST CANCER (MBC)

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Literature data coming from studies carried out in selected pts. and with the help of adequate supportive care have demonstrated a steep dose-response relationship for anthracyclines in the treatment of MBC. The aim of the present study was to verify if a relative aggressive treatment could be employed in the everyday medical practice on an outpatient basis. From February 1991 to March 1994, a series of 66 women with MBC coming from 7 oncology units was treated with a chemotherapy regimen containing epirubicin (100 mg/sqm, day 1) and cyclophosphamide (600 mg/sqm, day 1); courses were repeated every 3 weeks to a maximum of 6. The median age of pts. was 52.5 yrs. (range 28-71) and the median Karnofsky P.S. 80 (range 40-100). Twenty pts. were premenopausal (30.3%) and 45 postmenopausal (68.1%); 32 (48.5%) received previous adjuvant chemotherapy and 34 (51.5%) were chemotherapy naives treated either with surgery or radiotherapy. Metastatic sites were viscera (63), bones (39) and skin (17) with more than 1 in most cases. On the whole, 351 cycles have been administered with a median of 5.3 (range 2-6) per pt. Two pts. are not evaluable for activity (1 early death, 1 protocol violation). Out of 64 evaluable pts., 14 reached a CR (21.9%) and 34 a PR (53.1%) with an overall RR of 48/64 (75.0%). Eleven pts. had stable disease (17.2%) and 5 (7.8%) went into progression. The treatment was very well tolerated: grade 1-2 leukopenia was observed in 43.9% of cycles and grade 3-4 in 2.3%. Other toxicities were grade 1-2 nausea/vomiting (65.5% of cycles) and alopecia in 91% of pts. No cardiac toxicity was recorded. It can be concluded that a moderately aggressive chemotherapy in outpatients can be easily used with positive outcome both in terms of activity and safety.

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SERUM CA 15-3 IN NODE-NEGATIVE BREAST CANCER: A MARKER OF PROGNOSTIC SIGNIFICANCE?

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Concentrations of CA 15-3 antigen were measured at diagnosis in the sera of 90 node-negative breast cancer women. CA 15-3 values correlated with the higher histological grade ($p<0.02$), the low contents of estrogen ($p<0.01$) and progesterone ($p<0.001$) receptors. No association was found between CA 15-3 and tumor size. In univariative analysis of patients who completed 24 months follow-up (median 37,range 24-51), cases with CA 15-3 over 30.0 U/ml had a shorter disease-free and overall survival tah those with CA 15-3 within the normal range, but differences were only slghtly significant ($p<0.05$). These preliminary results justify further investigations to assess prognostic value of CA 15-3 in patients with node-negative breast cancer.

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BREAST CONSERVATION WITHOUT AXILLARY DISSECTION.

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Starting from the evidence that surgical treatment of the axilla does not in itself improve the survival of patients with small size breast cancer (<12 mm), and that the removal of clinically uninvolved axillary nodes is thus purely informative, we have designed a multicentric study on patients ≤45 years of age with clinically N0 breast cancer, 12 mm or less; the aim is to determine whether radiotherapy (RT) to the axilla reduces the risk of late appearance of nodal metastases. Patients treated by classic quadrantectomy without axillary dissection are being randomized to two arms: one receives RT to the breast only, and the second receives RT to breast (50 Gy + 10 Gy boost) and the axilla (50 Gy). The trial started on February 1st, 1995 and at 30th January 1996, 56 patients had been enrolled: 22 received RT to the axilla and 29 to the breast only. Of the 48 patients operated on at the EIO, 5 had a tumor ≤5 mm, 41 between 6-10 mm and 2 =11 mm. The proliferative index (Ki67) was <20% in 25 patients, and tumor grading was G1 in 23 patients, G2 in 20 and G3 in 5. In the absence of lymph node information, tumor grading, hormonal receptor status and proliferative were chosen to decide adjuvant treatment. Forty one patients received hormonotherapy, 2 chemotherapy and 6 no therapy. To achieve a statistical power of 80% at least 300 women will have to be randomized over 3 years and followed for a further 8 years. Also participating are the Rome, Parma, Florence, Naples and Turin centres of the Italian Senological Oncology Group (GrISO).

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COMBINATION OF CISPLATIN, EPIRUBICIN AND FTORAFUR FOR BREAST CANCER

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21 patients with locally advanced or metastatic breast cancer received Cisplatin 60 mg/m.sq. i.v., Epirubicin 50 mg/m.sq. i.v. every 3 weeks and Ftorafur 1200 mg p.o. daily. On the farmacokinetics study it was found that Ftorafur is absorbed with T1/2 abs about 7,8±3,5 hours. The best dose schedule is 400 mg x 3 per day. At this schedule concentration of Fluorouracil is equal to 0,13±0,03 mkg/ml. Concentration at steady-state (Css) for Ftorafur the 400 mgx2 per day is achieved during 6 days and is equal to 18±3 mkg/ml and in the schedule 400 mg x 3 per day - during 1,5 days (Css = 23 ± 3 mkg/ml).
Complete + partial response was achieved in 57% of patients. The adverse events in this combination were insignificant. Neutropenia grade III-IV - 19%, diarrhea 9%, stomatitis 19%, dermatitis 1%, nausea and vomiting 38%. Combination of Cisplatin, Epirubicin and Ftorafur can be used for neoadjuvant chemotherapy in breast cancer.