103 P

INDUCTION OF EXPRESSION OF TUMOUR TGFβ$_2$ MRNA IS ASSOCIATED WITH RESPONSE TO TAMOXIFEN IN BREAST CANCER.

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Tamoxifen is important therapy for postmenopausal patients with breast cancer. Whilst effects are largely mediated via the oestrogen receptor (ER), the growth suppressive effects of transforming growth factor betas (TGFβs) may also be involved. Expression of the isoforms of TGFβ mRNA has been measured by RNAase protection assay in 37 breast cancer patients treated with tamoxifen. All tumours expressed the isoforms both before and after treatment, and semi-quantitative assessment showed no consistent changes in TGFβ$_1$ or β$_3$ in either responding or non-responding patients. However, there was a significant trend for responding patients to show increasing TGFβ$_2$ expression (11/27) as compared to only 2/10 non-resonding patients (p=0.018), The present study suggests that response to tamoxifen may be associated with an increase in expression of TGFβ$_2$ mRNA in a proportion of breast cancers.

104 P

PREDICTIVE FACTORS FOR RESPONSE TO NEOADJUVANT CHEMOTHERAPY IN OPERABLE BREAST CANCER > 3 cm.

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A single institution study investigated the effect on objective response of 3-4 cycles of q 21 HD-Epirubicin or FEC$_{50}$ or q 14 (+G-CSF) HD-Epirubicin or FEC or MMM, according the following factors: ER (+/-), PgR (+/-), Ki-67 L.I. (+/-), SBR grading (G_2/G_3) and menopausal status (pre/post), in 53 pts, mean age 47 years (32-71), 26 premenopausal, 36 $T_{2>3cm}$, 17 T_3, 25 ER^+, 21 PgR^+, 14 Ki-67 L.I.$^+$, 38 G_2, 15 G_3. **Clinical results**: in T_2 group CR was achieved in 13.8%, PR>50% in 55.4 % and PR<50% in 30.6%; in T_3 group there was no CR, 70.1% PR>50%. and 29.9% PR<50%. **Univariate and multivariate analises** were performed to evaluate the real relative influence of each prognostic factor in response. Significance of associations was tested by the chi-square test.

Univariate: Linear regression= independent variables vs response					
	Ki-67 L.I.	**Menopause**	**PgR**	**G**	**ER**
t	1.69	2.58	2.25	- 1.92	- 1.85
p	0.028	0.061	0.069	0.096	n.s.
Linear discriminant function					
	Ki-67 L.I.	**Menopause**	**PgR**	**G**	
p	0.0665	0.0738	0.1071	0.1471	

Our data demonstrate that four out of five considered variables have been proved useful in predicting the right place of each patient in the responder (Ki-67 L.I.$^+$, Premenopause, PgR^+, G_3) or non responder group (Ki-67 L.I.$^-$, Postmenopause, PgR^+, G_2) in 42 out of 53 (79.24%) patients. These groups are determined by the value defined in the following equation: Response = 1.648 (costant) + PgR (1.010) - Ki-67 L.I. (1.277) - G (0.974) + Menopause (1.085) with a predictive power of - 0.351 for the responder group (CR + PR>50%) and 0.812 for the non responder.

105 P

TWO INTENSE ADJUVANT REGIMENS IN HIGH RISK BREAST CANCER PATIENTS WHO RECEIVED NEOADJUVANT.

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Our pilot study intended to compare the feasibility and efficacy of two adjuvant chemotherapy regimens in high-risk breast cancer pts (**large size + > 7 positive nodes) pretreated** by neoadjuvant chemotherapy (standard or accelerated by G-CSF) and surgery. **Twenty pts** (mean age 51.5; PS 0-1), 9 premenopausal, 12 ER^+, 7 PgR^+, 4 Ki-67 L.I.$^+$, 14 SBR G_3, T_{3-4}, N_{1-2}, M_0 (the two arms were balanced by these prognostic factors) were allocated 3-4 weeks after surgery to either Epirubicin 120 mg/m^2 q 21 x 3 times followed by CMF 1-8-28 x 3 times (**10 pts, ARM A**), or CTX 100 mg/m^2 p.o. qd x 7, EpiDoxo 50 mg/m^2 i.v., VCR 1 mg i.v., MTX 100 mg/m^2 i.v. on day 1 followed 20 hrs later by a 2-hr infusion of 5-FU 600 mg/m^2 i.v. and Leucovorin 10 mg/m^2 p.o. every 6hrs x 6, alternated every other week with a 48-hr infusion of 5-FU 300 mg/m^2 qd on day 8-9, x 16 weeks (**10 pts, ARM B**). WBC and absolute neutrophil count NCI g 2-4 TOXICITY was observed in 8.4% of pts in ARM A and 15.2% in ARM B ($p < 0.05$); g 2-4 anemia (Hb) in 22.3% in ARM A and 49.3% in ARM B ($p < 0.05$); g 2-3 thrombocytopenia in 6.7% in ARM B. Myelosuppression significantly delayed the planned dose (from 2 to 6 weeks; median 4) only in ARM B, so that the actual dose delivered was 75% in spite the routine G-CSF support. Grade 2 alopecia, was found in 100% of pts in the 2 arms; neutropenic fever in 7% and catheter complication in 10% of ARM B. Emesis were equally observed in the two groups both acute (6% - 5%) and delayed (15% - 18%). At median follow up of 24 months 3 loco-regional and 2 distal recurrences in ARM A and 1 and 1 respectivelly in ARM B were observed. Overall and disease-free actuarial survival were 100% and 68.57% (95% C.I. = ± 29.59) in ARM A and 100% and 83.33% (95% C.I. = ± 29.82) in ARM B. In our pretreated pts the two employed regimens were feasible even if in the 16-week the main peculiarity of the dose intensity had not fully preserved.

106 O

SITAM-01 ADJUVANT BREAST TRIAL FOR PATIENTS > 50 YEARS.

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This pragmatic, large scale randomised trial was designed after considering the evidences emerged from the 1985 systematic overiew of all trials about adjuvant tamoxifen in women with early breast cancer, also confirmed in the 1990 systematic overview, that have demonstrated a highly significant improvement in 10-years survival. For the patients over the age of 50, the main question addressed in this protocol is whether the duration of tamoxifen therapy affects disease-free on overall survival. However, it is not yet known how long women with breast cancer should continue to take adjuvant tamoxifen. The obvious question, for this trial started in 1988, is whether a longer period, say 5 years, is more beneficial. For the protocol of this study all women > 50 years and < 70 years with "operable" breast cancer, irrespective of nodal or menopausal status, where eligible. After primary therapy all patients were registered into the study through the coordinating center and received 20 mg tamoxifen daily for 2 years and, if they remained disease-free, were eligible for randomisation to stop or continue therapy for further 3 years. This protocol also permitted optional randomisation of patients to systemic chemotherapy or control, since there was little evidence, at that time, as to wheter additional benefits would be gained by using both chemotherapy and hormone therapy. This trial is the biggest trial about adjuvant treatments ever conducted in Italy, having recruited 2511 patients until January 1998 from 53 participating centers, of which 1722 were randomised to stop (862) or to continue (860) treatment. After 2 years of therapy, 16% of patients were not eligible for randomisation because they had relapsed and 4% had refused randomisation. Overall 1083 (47%) patients are N+ (139 of them with >3 nodes involved), 295 (12%) patients underwent adjuvant chemotherapy, 1277 (56 %) patients are ER+, 374 (16%) ER-, 105 (5%) ER borderline and 524 (23%) did not perform the determination of the ER status (data not yet available for 231 patients). 10.5% of the patients has experienced side-effects attributable to the hormone-therapy. After a median follow-up of 36 months, 1967 (78.4%) patients are disease-free, 147 (5.8%) have relapsed, 48 (1.9%) have developed a second tumour (7 endometrial cancer), 178 (7.1%) have died and 171 (6.8%) have been lost to follow-up.

107 P

Results of a randomized adjuvant breast cancer trial comparing a conventional with a perioperative start of chemotherapy.

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Purpose: The rationale of the present study was to validate the hypothesis of a favorable influence of a perioperative start of adjuvant chemotherapy in patients with operable breast cancer of various prognostic groups, as suggested by results of experimental data.
Patients and methods: Patients with operable breast cancer were entered into a prospective trial and randomized to receive epidoxorubicin (20 mg/sqm) and cyclophosphamide (200 mg/sqm; EC) either on days 1, 8 and 15 (= perioperatively) or on days 22, 29 and 36 (= postoperatively), day one being the day of surgery. Patients with lymph node involvement (N+, pre- and postmenopausal) and premenopausal patients without lymph node involvement (N-) and estrogen receptor (ER) negativity received 3 additional cycles of adjuvant chemotherapy with cyclophosphamide, methotrexate, fluouracil (CMF). All ER+ patients received 20 mg tamoxifen per day for two years.
Results: No increased toxicity or problems with wound healing were found in patients from the perioperative group. With a present median follow-up of 70 months, 76 out of 221 (34%) eligible patients have relapsed. The estimated percentage of disease-free survival (DFS) at 5 years was 66 (±3.2) in all patients, 59 (±5.4) in patients from the perioperative and 72 (±4.2) in those from the postoperative groups (p=0.09).
Conclusion: An advantage in DFS resulting from an earlier start of adjuvant chemotherapy than on postoperative day 22 can be excluded at this point of the study.

108 P

HISTOLOGICAL AND CLINICAL RESPONSE EVALUATION TO PRIMARY CHEMOTHERAPY IN LOCAL - ADVANCED BREAST CANCERS

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PURPOSE: To evaluate the curative potential of primary chemotherapy in term of clinical, histological response and survival in local-advanced breast cancers.
PATIENTS AND METHODS: 76 patients with local-advanced breast cancers (stage IIIA - IIIB) were treated in two sequences: group A: 29 patients with 4-6 cycles (CMF/FEC) chemotherapy, local-radiotherapy and surgery; group B: 47 patients with radiotherapy and surgery.
Two types of histological response (H.R.) have been individualized in 76 radical mastectomy specimens: complete HR without microscopic disease and incomplete HR, with residual tumor cells or histological tumor structure.
An univariate analysis of six prognostic variable (age, Karnofski performance status, clinical, histological response and therapeutical sequence) was performed using Kruskall-Wallis and Kaplan-Meier method.
RESULTS: 6 clinical complete responses (CR), 8 complete histological responses (HR) and 38% mortality rate was find in group A and 0 cases of complete HR and a 68% mortality rate at 36 weeks in group B. This difference is statistically significant (p=0,002 for CR and p=0,005 for HR).
The performance status at the diagnosis moment proved to be statistically significant for the clinical response and survival.
CONCLUSION: Neo-adjuvant chemotherapy in local-advanced breast cancers is effective in local control and survival.