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POSTER

COMPARISON OF 3 NEOADJUVANT CHEMOTHERAPY REGIMENS FOR OPERABLE BREAST CANCER

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In order to avoid modified radical mastectomy a neoadjuvant approach was adopted in our institute for non-inflammatory tumours. From 01/88 to 12/94, 238 patients (pts) received as primary chemotherapy 3 different regimens (all doses mg/m²): (1) AVCF/AVCFM, 126 pts (adriamycin 30, vincristine 1 d1, cyclophosphamide 300, fluorouracil 400 d2-d5 and methotrexate 20 d2 and 4, every 28 d); (2) NEM, 69 pts (navelbine 25, epirubicin 35, methotrexate 20 d1 and d8, every 28 d) and (3) TNCF, 43 pts (THP-adria 20, d1-3, navelbine 25 d1 and d4, cyclophosphamide 300, fluorouracil 400 d1-d4, every 21 d). In spite of good results with AVCF, the new combinations with navelbine seemed promising (NEM regimen concerned mainly stage II and TNCF stage III tumours): they were all operated for (2) and (3), partially for (1), and showed a progression in pathological complete response rate (pCR). Evaluation comprised 3 methods: clinical (C), echographic (E), mammographic (M). If breast conservation rate (85/85/77%) was quite similar in the 3 regimens, the overall objective response rate (C: 85/73/93; E: 75/66/85; M: 58/59/80%) and more importantly pCR (7/16/26%) increased with regimens 2 and 3, with a rise in toxicity with TNCF (ASCO 1995, abst. 218). If cases where remains only "in situ" are added, pCR reached 21% with NEM and 28% with TNCF. These navelbine-anthracyclins associations and dose intensity improved pCR, but the impact on survival has to be confirmed.

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HD-EPI AND FEC REGIMEN IN NEOADJUVANT CHEMOTHERAPY FOR PRIMARY BREAST CANCER

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From Jan. 1991 to Dec. 1994, two cohorts of 33 consecutive women with primary breast cancer, with large tumors (T2 > 3 cm or T3, N0-N2, M0), received primary chemotherapy (3.3 pts. on FEC: FU 500 mg/m² day 1-8, EPI 75 and CTX 500 mg/m²/iv on day 1; 33 pts. on HD-EPI: 120 mg/m²/iv day 1) administered every 3 week for a total of 3 cycles. Modified radical mastectomy was chosen in pts with T > 3 cm in diameter at surgery, while QUART (after Veronesi *et al.*, 1981) was performed when T at surgery was <3 cm. The tumor shrinkage and type of surgery were

	Initial T (cm)	N	T at surgery (cm)	QUART	%
			<3	>3	
FEC regimen	3.0-4.0	8	7	1	7/8 87.5
	4.1-5.0	8	6	2	6/8 75.0
	5.1-6.0	8	5	3	5/8 62.5
	>6	9	3	6	3/9 33.3
		33	21	12	21/33 63.6
HD-EPI regimen	3.0-4.0	9	9	0	9/9 100
	4.1-5.0	9	8	1	8/9 88.8
	5.1-6.0	10	6	4	6/10 60.0
	>6	5	2	3	2/5 40.0
		33	25	8	25/33 75.7

HD-EPI seems slightly more effective than FEC regimen in reducing primary tumor size and thus allowing the substitution of conservative for mutilating surgery.

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THERAPY-RELATED ACUTE MYELOID LEUKAEMIA FOLLOWING ADJUVANT CHEMOTHERAPY FOR BREAST CANCER USING MITOXANTRONE AND METHOTREXATE WITH OR WITHOUT MITOMYCIN

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AML following adjuvant CMF for breast cancer is rare, late, and associated with total dose of cyclophosphamide and further leukaemogenic therapy. The 3M combination (mitoxantrone, methotrexate, mitomycin

offers equal efficacy to CMF in advanced disease and more acceptable toxicity. The 2M combination omits mitomycin and is felt to have equal efficacy. From 1986-92, 3M and 2M were given as adjuvant therapies to 60 premenopausal patients aged 32-54 years (median 42). They had node-positive disease or a local recurrence resected without systemic disease. Thirty had 3M, (projected total doses per m² BSA of mitomycin 32 mg, methotrexate 240 mg and mitoxantrone 64 mg). Mitomycin was given every six weeks, the other drugs every three weeks over 24 weeks. Thirty received 2M (projected total doses of 280 mg/m² for methotrexate and 96 mg/m² mitoxantrone), every three weeks over 24 weeks. Percent projected dose received was 88.6% mitomycin, 92.9% methotrexate and 96% mitoxantrone. From 1993 reports of early AML following 3M in advanced breast cancer appeared and we studied this phenomenon following 3M and 2M in the adjuvant setting. Two cases of AML, FAB M2 and M4EO without detected cytogenetic abnormalities have occurred 18 and 23 months following 2M therapy. Neither patient had other leukaemogenic treatment. Hitherto mitomycin has been considered the major risk factor but given the acknowledged risk associated with topoisomerase I agents, mitoxantrone must be considered a likely causative agent here and its use in adjuvant treatment regimens cannot be recommended.

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IMPROVEMENT OF PROGNOSIS IRRESPECTIVE OF AGE IN EARLY NODE NEGATIVE EARLY BREAST CANCER BY ADJUVANT HIGH-DOSE MEDROXYPROGESTERONE ACETATE (HD-MPA); TEN YEARS RESULTS OF A MULTICENTER RANDOMIZED TRIAL

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Two-hundred-and-sixty node negative early breast cancer patients, among whom 246 were fully evaluable were randomized, after adequate surgery, to receive either no further medical treatment (group A) or an endocrine therapy with HD-MPA (500 mg IM daily for 4 weeks then 500 mg twice weekly for the next 5 months) (group B). Patients at cardiovascular or thrombo-embolic risk were excluded. Radiotherapy was optional in mastectomized subjects but mandatory after limited surgery. Patients characteristics were well balanced among both groups. Toxicity was manageable (weight increase in most patients and usual side-effects linked to progestin use in a maximum of 16% of patients in group B). In this group, an unexpected death, due to lung fibrosis and CMV infection 2 months after radiotherapy was reported. At 10 years median follow up, relapse free survival (RFS) was significantly improved in HD-MPA arm (A: 0.59 vs B: 0.66 - P 0.005 - 0.02). This was observed for the whole group as well as in all prognostic sub-categories (age <50; ≥ 50; menopausal status; T; receptor categories; type of surgery). Differences were less striking at 10 years than at 5 years peculiarly due to the fact that in ≥ 50 years patients, RFS curves tended to join. On the contrary in <50 years patients, the gain in RFS was maintained all along the study period (at 5 years: A: 0.68 vs B: 0.87; at 10 years: A: 0.42 vs B: 0.68). These differences in RFS were translated in a survival benefit in younger patients. Multivariate analysis evidenced as independent variables only the tumor stage (T) and the treatment (A/B). In conclusion, a clearcut adjuvant impact of HD-MPA was evidenced namely in >50 years early breast cancer, i.e., in premenopausal patients. This observation requires further randomized evaluation versus castration or tamoxifen.

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MITOXANTRONE AND METHOTREXATE (2M), A NEW CHEMOTHERAPY REGIMEN FOR BREAST CANCER THAT CAN BE SAFELY COMBINED WITH TAMOXIFEN

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The combination of mitoxantrone 7 mg/m² IV 3 weekly, methotrexate 30 mg/m² IV 3 weekly and mitomycin C 7 mg/m² IV 6 weekly (3M) has been shown to be as effective as anthracycline based combination chemotherapy in metastatic breast cancer. In the treatment of primary breast cancer the addition of tamoxifen to chemotherapy may be beneficial. As primary medical treatment for operable breast cancer we therefore used 3M plus tamoxifen 20 mg/day (3MT). Unfortunately, an interaction between tamoxifen and mitomycin C caused the haemolytic uraemic syndrome. Therefore we stopped using mitomycin C and increased the mitoxantrone dose. The regimen now is mitoxantrone 11

mg/m² and methotrexate 30 mg/m² both IV 3 weekly plus tamoxifen 20 mg/day (2MT).

59 patients have received 3MT and 66 have received 2MT as primary medical treatment. The 3MT and 2MT regimens resulted in no palpable abnormality in 10 (17%) and 16 (24%) of patients respectively and in only minimal residual nodularity in 23 (39%) and 17 (26%) of patients respectively. (No significant difference). Both regimens resulted in an overall response rate of 85%. We have observed no evidence of haemolytic uraemic syndrome with 2MT.

Therefore 2M is an effective, easy to give chemotherapeutic regimen which in the treatment of primary breast cancer can be safely combined with tamoxifen.

58 POSTER OPERABLE BREAST CANCER IN WOMEN UNDER FORTY YEARS

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The aim of this study was to determine whether breast cancer in women under forty has a poorer prognosis as compared to cancers occurring in older premenopausal women.

From January 74 to December 90, 658 premenopausal women underwent surgery as first treatment for operable breast cancer (invasive ca., first single breast primary cancer, no personal history of invasive cancer, no inflammatory sign, tumor size under 7 cm). One hundred and thirty-nine patients were under 40 years old.

Adjuvant treatment was determined according to nodal status: axillary node positive patients received chemotherapy and/or hormoneotherapy (ovarian suppression).

Patients' characteristics (T, N, histologic grade, hormone receptors) are equal in both groups under and above 40 years. Median follow-up is 10 years.

Overall survival is not significantly different between women under and above 40 years of age. On the other hand, disease free survival is shorter for women under 40 ($P = 0.01$). This difference is not explained by a more intensive follow-up after treatment for younger patients and prompted us to intensify or to respect dose intensity.

59 POSTER TAMOXIFEN (TAM) IN BREAST CANCER (BC): TOXICITY OF LONG TERM ADJUVANT TREATMENT

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To evaluate collateral effects of a TAM prolonged treatment, we analyzed, in a retrospective study, 243 pts, whose mean age was 59.2 years (27-85), all BC treated with radical surgery and adjuvant TAM for more than 2 years, 61/243 in premenopausal (25.1%) and 182/243 in postmenopausal age (74.9%). Twenty-nine out of 243 pts (11.9%) had a precedent hysterectomy for other benign gynaecological diseases. Forty-three pts (17.7%) received TAM 20 mg/die and 200 (82.3%) 30 mg/die; median treatment duration was 50.5 months (24-120 m) (from 2 to 3 years: 58 pts, from 3 to 4 years: 39 pts, from 4 to 5 years: 97 pts, >5 years: 49 pts, in which TAM was readministered as first line too). The median follow-up was 70.3 m (2-15 years). For intolerance, 22 (9.1%) pts reduced TAM from 30 to 20 mg/die while 12 (4.9%) pts stopped for the same problem. We reported these side effects: thrombophlebitis in 13 pts (5.3%), epigastralgia of mild entity in 18 pts (7.4%), leucopenia grade I WHO in 5 pts (2.1%), thrombocytopenia grade II in 2 pts (0.8%), mild hyperglycemia in 15 pts (6.2%), mild nausea in 8 pts (3.3%), leukorrhea in 5 pts (2.1%), flashing in 12 pts (4.9%), spotting from endometrial hyperplasia in 22/214 pts (10.3%). Only 3 pts had a contralateral BC (1.2%). We reported 4 gynaecological cancers (1.9%): 2 endometrial adenocarcinomas after 22 and 60 months of TAM treatment, 1 ovarian granulosa-cells tumor after 30 months and 1 ovarian tumor-not style typized after 60 months. Two pts (0.8%) had gall-bladder cancer (1 pt after 52 months; 1 pt after 67), 1 pt (0.4%) had a stomach cancer after 6 months interruption of therapy with TAM for 96 months, 1 pt (0.4%) had a pancreas cancer after 51 months. In conclusion, our results reflect the literature about the risk of a secondary endometrial cancers in long term treated pts (*Lancet* 1989, i, 117); the correlation between TAM and endometrial cancer is sure; there is no evidence of correlation with other tumors. We suggest periodic gynaecological control in patients treated with TAM for more than two years.

60 POSTER TAMOXIFEN AND TOREMIFENE: THE BENEFICIAL HYPOLIPEMIC EFFECT IN WOMEN IS MEDIATED BY CHOLESTEROL BIOSYNTHESIS INHIBITION

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Tamoxifen (TAM) is an effective antiestrogenic anticancer drug. In long-term therapy it decreases serum cholesterol and LDL-cholesterol levels and decreases the risk of coronary artery disease. The mechanism of the hypolipemic effect has not been fully elucidated. Toremifene (TOR) is a new antiestrogenic anticancer drug that has clinical efficacy equal to that of TAM. The structure of TOR is closely related to that of TAM and animal experiments suggest that also TOR can have hypolipemic effects. The effect of TAM and TOR therapy on serum lipid levels were studied in postmenopausal advanced breast cancer patients. The effect on cholesterol biosynthesis was evaluated by measuring cholesterol precursor levels by gas-liquid chromatography at pre-dose and after 2, 6 or 12 months therapy. Both drugs decreased cholesterol and LDL-cholesterol levels almost equally. This suggests that also TOR can be expected to have TAM-like beneficial antiatherogenic effect during long-term therapy. Of the cholesterol precursors Δ^8 -cholesterol level was increased up to about 50-fold with both drugs; in other precursor levels only minor changes were seen. This indicates that these antiestrogens inhibit Δ^8 -cholesterol conversion to lathosterol and as a result the cholesterol biosynthesis is downregulated. This inhibition is suggested to be the main method for the hypolipemic effect of these drugs.

61 POSTER ENDOMETRIAL CANCER INDUCTION BY TAMOXIFEN IN THE RAT

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Tamoxifen (TAM) is an antiestrogenic breast cancer drug. Medication with TAM increases the risk of secondary cancers in the endometrium. In the rat TAM is a strong hepatocarcinogen. Toremifene (TOR), a new antiestrogen clinically as effective as TAM, has not shown any hepatic or endometrial adverse effects. We studied the effects of TAM and TOR on rat endometrium. Three separate studies were put together. Female SD-rats were daily treated with vehicle or with the drugs at equimolar doses (20 or 80 $\mu\text{mol/kg}$) p.o. for 13-52 weeks. Both drugs produced comparable uterine atrophy and weight reduction at both dose levels indicating an equal hormonal effect. No preneoplastic or neoplastic changes were observed in control or TOR groups or in the low-dose TAM group. The incidence of squamous cell metaplasia with prominent keratinization was 10% in the high-dose TAM group. In 3 of the metaplasias there was a focal dysplastic change and two of these animals bore also a focal invasive squamous cell carcinoma. The carcinomas were found after 20 or 26 weeks of dosing, in both cases after a recovery period. The histopathological outlook of these lesions argued against a mere hormonal etiology. TOR produced no lesions although the estrogen antagonist/agonist activities and the endometrial proliferative potentials of these two drugs at the dose levels used are closely comparable. In conclusion, a nonhormonal (possibly genotoxic) mechanism in the TAM-induced endometrial carcinogenesis is probable. TOR might be more safe clinically, especially when healthy women are treated with antiestrogens in breast cancer preventive indication.

62 POSTER NEOADJUVANT CHEMOTHERAPY FOR STAGE III PRIMARY BREAST CANCER

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Neoadjuvant chemotherapy is showing promising results in the primary treatment of breast cancer. We have analysed the data on 91 patients (age 30-78 years) representing 15 years of experience from 1980-1995 in our unit. All patients had advanced tumours, 69% being T4 (46% of these inflammatory), with 76% of tumours more than 5 cm in size and 68% clinically node positive at diagnosis. Four chemotherapy regimens have been used: (1) Ariamycin 40 mg/m² + Vincristine 1 mg/m³ \times 3 cycles. (2) Mitozantrone 14 mg/m² \times 3 cycles. (3) Cyclophosphamide