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THROMBOEMBOLIC ACCIDENTS (T.E.A.) IN POSTMENOPAUSAL WOMEN TREATED BY ADJUVANT TAMOXIFEN (TAM) : 19 CASES REPORTS

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A slight increase of T.E.A. in women treated by TAM was already observed, but in the large majority of the cases, patients underwent also chemotherapy or had metastases. From 1980 to 1990, among 441 post-menopausal women treated by adjuvant TAM for breast cancer (BC) by conservative approach, we observed 19 TEA (4.3 %), 1 to 34 months after treatment onset. All received adjuvant TAM at 20 mg/d (70 %) or 40 mg/d (30 %) with a median duration of 36 months. All women were in remission at the moment of T.E.A.
The median age of these patients was 64 years. We observed 9 pulmonary embolism (P.E.), 9 deep venous thrombosis and an acute ischemic syndrome of the leg by arterial obliteration. One woman, 74 years old, died by massive bilateral P.E. confirmed by autopsy. In the other cases T.E.A. were reversible with anticoagulant treatment and surgical operation in two. In 10 cases, TAM was stopped. Six women had risk factors of T.E.A., such as previous phlebitis, varicose veins or cardiac disease. Moreover, an aggravating or inducing factor was found in 10 cases (infection in 2 and surgical operation for benign disease in 8). Interestingly, 8 out 19 women (42 %) had lobular B.C., while this histological type represented only 9 % of all the patients. In spite of absence of randomisation, no T.E.A. was observed in the 125 postmenopausal women without adjuvant TAM.
Our study confirms the potential increased risk of T.E.A. during TAM adjuvant treatment in post-menopausal women. Thus, a careful selection of the patients seems necessary to evaluate the benefit/risk ratio. Women with previous history of cardiac disease (especially rhythm disorders, cardiac failure) and especially T.E.A. should avoid antiestrogen therapy. Additionally caution is necessary in all situations (medical or surgical) favouring the prolonged bed rest. A temporary suspension of the TAM (2-3 months) in these "risk situations" should be proposed. In addition, our data suggest a particular risk in women with lobular cancer. All these points must be carefully examined especially in the new prospective chemoprevention trials enrolling healthy women with high risk of B.C.

Key words : Tamoxifen - Pulmonary embolism - Thrombosis

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TUMOUR RESPONSE TO PRIMARY CHEMOTHERAPY PREDICTS BREAST CONSERVATION AND SURVIVAL

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390 evaluable breast cancer patients had been randomized to receive either 4 cycles of neoadjuvant chemotherapy (CAF) (n=200) or the same chemotherapy in a conventional setting subsequent to primary irradiation (n=190). In a forward selection procedure using the proportional hazards model we tested for the impact of 11 candidate variables on survival. Variables associated with prognosis in the present population were clinical node status (RR:2.9), neoadjuvant chemotherapy (RR:1.9) pathological grade (RR:1.9) and tumour size (RR:1.8). Primary chemotherapy remained significantly associated with a better survival after adjustment to other variables (RR:1.9; CI:1.08-3.46) as compared to the conventionally timed treatment.
191/200 patients were evaluable in the neoadjuvant arm and we screened for correlations between clinical response and other clinical or biological criteria. Association profiles showed high S phase to be strongly predictive of chemosensitivity (p = 0.003). Kaplan-Meier estimates showed improved four year survival rates for responding patients following two (p=0.01) months of chemotherapy. An objective response at two cycles might also be shown to be predictive of an improved metastases free interval, but failed to reach statistical significance at a median follow up of 46 months (p=0.07). Patients whose tumours showed a major or complete regression to primary chemotherapy were equally more likely to have a breast conservation (p=0.0016). Local recurrence rates were not influenced by response to treatment following two cycles, since non-responders had more frequently surgery as part of their primary treatment.

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RANDOMIZED TRIAL OF ADJUVANT CHEMOTHERAPY (CHT) (CMF vs. CAMF) IN NODE-POSITIVE (N+) BREAST CANCER.

OJEDA B; RUEDA A;LOPEZ LOPEZ JJ;ALONSO MC;PELEGRI A;BOVER I;VILADIU P;BELTRAN M;BATISTE-ALENTOR E;FABREGAT X;CATALAN G;SOLIS L;BADIA A;GALLEN M;BOLEDA M;RIFA J. Medical Oncology Unit. Hospital de la Santa Creu i Sant Pau. Barcelona (Spain). Between 1986 and 1990, 300 patients (p) with operable breast cancer, N+ and age<60 years were randomized to receive adjuvant CHT with CMF (at classical doses)/28 days (d) for 6 cycles or CAMF (cyclophosphamide 750 mg/m² d1, adriamycin 30 mg/m² d1, methotrexate 40mg/m² d8 and 5-FU 500 mg/m² d8)/28 d for 3 cycles.
The median of sampled N was 13; there were <4N+ in 157 p, 4-9N+ in 101 p and >9N+ in 42 p.
With a median follow-up of 51 mos (range,2-82) the 7 years overall and disease-free actuarial survival (OS and DFS) were:

	n°p	OS (CMF CAMF)	DFS (CMF CAMF)
All p	300	68% 55% p=0.1	49% 37% p=0.01
4-9 N+	101	65% 43% p=0.009	41% 28% p=0.009

There were no significants differences among the other N+ groups. When survival is stratified according to the number of N+ the differences were more significants for OS (p=0.005) and DFS (p= 0.0008). The multivariate analysis showed that the received CHT was an independent pronostic factor; CMF was superior for OS (B=1.92) and DFS (B=1.67) than CAMF.

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SECOND CANCER RISK FOLLOWING BREAST CANCER TREATMENT.

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Risk of second cancer was studied in a group of 6358 patients with non-metastatic breast cancer (BC) who were admitted to the NKI and the DDHK from 1976 till 1987. 99% of all patients were followed up till at least July 1989. Median follow-up time was 7.2 years. Preliminary analyses of 3093 patients from the NKI showed that 256 patients developed a second cancer (excl. basal cell carcinoma of the skin) as compared to 128 cases expected on the basis of cancer incidence rates in the general population (relative risk (RR):2.0; 95% confidence interval (CI):1.8-2.3). All second tumours were pathologically confirmed and a diagnosis of contralateral breast cancer (CLBC) was only accepted when no distant metastases had become manifest up to 2 months after CLBC diagnosis (n=152). Significantly increased relative risks were observed for CLBC (RR=3.6; 95%CI:3.1-4.2), soft tissue sarcoma (RR=7.4; 95%CI:2.0-19.0), malignant melanoma (RR=2.8; 95%CI:1.2-5.6) and ovarian cancer (RR=1.9; 95% CI: 1.0-3.2). Patients treated with radiotherapy (RT) had slightly higher risk (60%) of CLBC as compared to patients who only had a mastectomy (p=0.09). However, 10-year survivors who had received RT experienced ninefold risk of CLBC as compared to patients in the mastectomy only group (p=0.03). Patients who received hormonal therapy (HT; mostly tamoxifen) in addition to RT did not have decreased risk of CLBC as compared to patients who received radiotherapy without HT (RR=4.5 vs RR=3.8; p=0.44). Patients treated with RT and chemotherapy (CT; mostly CMF) also had similar risk of CLBC as had patients who did not receive CT (RR=4.3 vs RR=3.8; p=0.67). Among patients under age 50 (n=1464), the overall risk of CLBC was much higher (RR=5.8; 95%CI:4.6-7.1) than in patients of 50 years and older (RR=2.5; 95%CI:1.9-3.1). The relation with radiotherapy was stronger in the younger age group. During the ECCO 7 conference results will be presented for the entire cohort of 6358 patients.

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UPDATE OF THE ROYAL MARSDEN HOSPITAL TAMOXIFEN PREVENTION PROGRAMME IN HEALTHY WOMEN AT INCREASED RISK OF BREAST CANCER

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At the Royal Marsden we are undertaking a double blind, randomised, feasibility trial using tamoxifen 20 mgs/day versus placebo in over 1800 healthy women at increased risk of breast cancer. Estimated compliance at 5 years is maintained at about 80% for women on placebo compared to 70% for those on tamoxifen (p<0.05). Acute toxicity is similar for patients receiving tamoxifen or placebo. The reduction in total serum cholesterol is now maintained out to more than five years in pre and postmenopausal women with no evidence of any interaction between tamoxifen and hormone replacement therapy.
Bone density using single photon and dual energy xray absorption and sequential measurement of various clotting factors indicate no adverse effects. Sequential pelvic ultrasound examination indicate an increased incidencé of ovarian cysts and uterine fibroids. We are now continuing accrual to this trial to 2000 healthy women at the Royal Marsden Hospital. Multicentre trials have also started in the USA and Italy aiming to accrue a total of 50,000 women.

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A RANDOMISED TRIAL OF MAINTENANCE THERAPY FOR NON METASTATIC INFLAMMATORY BREAST CANCER (IBC).

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From january 1987 to may 1992 previously untreated patients with non metastatic IBC were entered in a multicenter randomised study to assess the effectiveness of maintenance treatment after complete remission (CR) completion with combined modality therapy. The principal criterion of assessment was the disease free survival (DFS) at 3 years. All patients received 3 AVCMF every 28 days : (adriamycine 50 mg/sqm i.v. d1, vincristine 0.7 mg/sqm i.v. d2, cyclophosphamide 300 mg/sqm i.v. d2-3, methotrexate 15 mg/sqm i.v. d2-3, 5-fluoro-uracile 450 mg/sqm i.v. d2-3). Then locoregional therapy include radiation (RT) +/- surgery (S) or S alone, on a cyclical schedule while continuing chemotherapy (CT) with 5 FAC every 28 days (F 500 mg/sqm i.v., A 50 mg/sqm i.v., C 500 mg/sqm i.v., d1). The patients in CR were then randomised between **arm A** with maintenance CT: 6 VM courses (etoposide 120 mg/sqm p.o. D1-3, mitomycine 8 mg/sqm i.v. d1) and **arm B**: no maintenance CT. 133 patients were enrolled in the initial part of the protocol. 112 were in CR and randomised: 54 in the armA and 58 in the arm B. 20 patients were not in CR and 1 died of toxicity. 106 out of 112 patients received the planned CT. Local treatment was RT alone in 92 cases, S in 5 cases and RT + S in 15 cases. **In the arm A** 26 patients out of 54 received 6 VM courses as planned. 28 received less than 6 courses either for toxicity (12), or relapse (5) or other causes (11). 22 patients developped metastasis and 12 local relapses. **In the arm B** 34 patients had metastasis and 15 local relapses. The DFS results from randomisation to june 1993 will be presented.