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## COMPARISON OF 3 NEOADJUVANT CHEMOTHERAPY REGIMENS FOR OPERABLE BREAST CANCER

*I. van Praagh, J.P. Ferrière, H. Curé, V. Feillel, G. Le Bouëdec, M. de Latour, C. Rolhion, S. Charrier, I. Assier, J.L. Misset, J. Dauplat, P. Chollet*
*Centre Jean Perrin and INSERM U71, B.P. 392, 63011 Clermont-Ferrand Cedex, and ICIG, Villejuif, France*

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/m$^2$): (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, cyclophoshamide 300, fluorouracile 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

*G.A. Da Prada, P. Preti, L. Pavesi, G. Fiore[1], P.L. Bertoli[2], G. Robustelli della Cuna*
*Division of Medical Oncology, Clinica del Lavoro Foundation, Pavia*
*[1]Division of Internal Medicine*
*[2]Division of Obstetrics & Gynecology, Osp. di Nova Ligure, Italy*

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/m$^2$ day 1–8, EPI 75 and CTX 500 mg/m$^2$/iv on day 1; 33 pts. on HD-EPI: 120 mg/m$^2$/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 | | |
| | 3.0–4.0 | 8 | 7 | 1 | 7/8 | 87.5 |
| FEC | 4.1–5.0 | 8 | 6 | 2 | 6/8 | 75.0 |
| regimen | 5.1–60 | 8 | 5 | 3 | 5/8 | 62.5 |
| | >6 | 9 | 3 | 6 | 3/9 | 33.3 |
| | | 33 | 21 | 12 | 21/33 | 63.6 |
| | 3.0–4.0 | 9 | 9 | 0 | 9/9 | 100 |
| HD-EPI | 4.1–5.0 | 9 | 8 | 1 | 8/9 | 88.8 |
| regimen | 5.1–60 | 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

*P.A. Daly, P. Cremin, M. Flattery, S.R. McCann*
*Department of Clinical Haematology and Oncology, St. James's Hospital and Trinity College, Dublin, Ireland*

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 m$^2$ 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/m$^2$ for methotrexate and 96 mg/m$^2$ 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

*C. Focan, M. Beauduin, E. Salamon, J. de Grève, G. de Wasch, J.P. Lobelle, F. Majois, A. Tagnon, J. Tytgat, S. Van Belle, R. Vandervellen, A. Vindevoghel*
*Adjuvant Breast Cancer Project, Belgium*

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 hormonotherapy 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 deplored. 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

*T.J. Iveson, T.J. Powles, A. Tidy, S. Ashley*
*Royal Marsden Hospital, Sutton, Surrey, U.K.*

The combination of mitoxantrone 7 mg/m$^2$ IV 3 weekly, methotrexate 30 mg/m$^2$ IV 3 weekly and mitomycin C 7 mg/m$^2$ 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