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**AFFINITY OF ANTIOESTROGENS AND (ANTI)-PROGESTINS FOR THE ANTIOESTROGEN BINDING SITE (AEBS)**

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Most breast tumours contain an antioestrogen binding site (AEBS). Its biological function is presently unknown, but it is conceivable that AEBS play a role in the development of resistance to antioestrogen. In view of the development of new antioestrogens and of reports on membrane bound progestin binding proteins, we compared the affinity of antioestrogens and (anti)progestins for rat liver AEBS. A 12,000*g supernatant was incubated with 8 nM of [3H]-tamoxifen (Tam) and increasing concentrations of competitors. The relative binding affinities were: Tam (ICI): 100; 4-hydroxy-Tam (ICI): 24; N-desmethyl-Tam (ICI): 9; Nafoxidine (Upjohn): 202; Clomiphene: 222; Toremifene (Farmos): 48; 4-hydroxy-toremifene (Farmos): 27; N-desmethyl-toremifene (Farmos): 9.1. The steroidal anti-oestrogen ICI 164,384, the antioestrogen Zindoxifene, its deacetylated metabolite D-15414 and the new antioestrogen D-18954 (all Asta) had a RBA below 0.05%. Progesterone, Org-2058 and 19-nor-21-fluoro-derivatives, antiprogestins Org 31376 and Org 31710 (all Organon), cholesterol and its 7-keto-, 7-beta-hydroxy-, and 3,7,12-alpha-trihydroxyderivatives also did not compete. It is concluded that the phenylalkylaminoethoxy side chain of tamoxifen and related compounds is important for the recognition by the AEBS.

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**ENDOMETRIAL SIDE EFFECTS WITH TAMOXIFEN FOR BREAST CANCER**

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Tamoxifen is the most widely used non-steroidal anti-oestrogen for adjuvant treatment of post-menopausal breast cancer. This agent is well tolerated and effective according to recurrence-free survival and overall survival data including recent meta-analyses. Today, long term therapeutic trials are performed with administration of this drug for 5 years, or more or even indefinitely. Mechanisms of action and pharmacology are incompletely understood. The antagonistic oestrogenic property (via competitive inhibition of oestrogen receptor) is associated with a partial agonistic oestrogenic effect and depends on the target tissue involved. Vaginal bleeding is not an uncommon symptom observed in women so treated. We have investigated abnormal uterine bleeding occurred among 26 patients receiving tamoxifen for breast carcinoma. The histopathological findings obtained by dilatation and curettage or hysterectomy, are the following:

- endometrial polyps and/or hyperplasic mucosa : 18 cases
- endometrial adenocarcinoma : 3 cases
- atrophic mucosa : 5 cases

This report highlights the potential oestrogen-like behaviour and carcinogenic risk towards endometrium with prolonged anti-oestrogenic administration. Metrorrhagia was explained by adverse stimulatory effect in 80 % of cases (21/26). In the litterature, the increased incidence of endometrial cancer could be related to the posology and duration of tamoxifen exposure.

Sonographic and hysteroscopic examinations are recommended with the aim of carefully following up the uterine corpus as long as polonged tamoxifen treatment is given.

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**NON METASTATIC BREAST CANCER**
**First line treatment with tamoxifen**

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Locally advanced breast cancer are usually treated with chemotherapy, because prognosis is overweighted by future wide-spread metastasis. For elderly women, the best treatment is often antiestrogens. They are prescribed either continuously for patients with poor general conditions *(group A)* or primarily before locoregional treatment by surgery and/or radiotherapy ; this treatment is either performed after secondary recurrence despite hormonal treatment *(group B)* or after maximal efficacy of hormonal treatment *(group C)*.

One hundred women (median age 72,6 years) with non metastatic breast carcinoma are retrospectively studied. Sixty-nine objective responses have been got with first line tamoxifen (30 mg/d) (10 complete responses) ; only 3 patients progressed and the others were stabilized. Objective responses occure after median follow-up of 5 months. Actuarial adjusted survival curves are identical for *group A* (palliative hormonal treatment) and *group C* (locoregional treatment after response to hormonal treatment) but are better than *group B* (locoregional treatment after secondary failure of hormonal treatment) (p=0,01 and p=0,0003 respectively - log rank test).

This retrospective analysis allows to realize a randomized trial comparing hormonal treatment to hormono-chemotherapy for menopausal patients with operable breast cancer bigger than 4 cms, before adjusted locoregional treatment.

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**TAMOXIFENE (TAM) AND PRIMARY BREAST CANCER IN OLD WOMEN**

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Between April 1987 and December 1989, 311 women over the age of 70, with operable breast cancer (b.c.), were randomized to Surgery + Tam (20 mg/d for 5 yrs) or Tam (160 mg d 1, followed 20 mg/d till progression). The median f.up was 13 mos, the mean age of pts was 76 yrs. The two groups were well balanced for tumor size, concomitant diseases and performance status. In the Tam group 27 pts (18.1 %) developed local progression, with 5 cases followed by distant metastases (Ml). The overall incidence of Ml was 10 (6.7 %). Nine pts (6 %) died: two for intercurrent diseases (i.d.) free of Ml, two for i.d. with Ml, five for b.c.. In the Surgery group 13 pts (10.1 %) developed Ml. Four pts (3.1 %) died, of whom two for b.c..

In pts over 70 yrs, with primary breast cancer, Tam alone appears to be able to provide local and systemic control of the disease in 80 % of cases. In case of local progression, IInd line Surgery or Radiotherapy may control the disease in further 14 % of cases. If further f.up will confirm these data, Tam could be an interesting first line therapy in such patients.