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REGRESSION OF OESTROGEN-INDUCED PITUITARY HYPERPLASIA AFTER CHRONIC TREATMENT WITH SANDOSTATIN (SMS 201-995) IN THE RAT

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Sandostatin® is a very potent and long-acting analogue of somatostatin (SRIF). Both compounds are capable of inhibiting prolactin secretion in animals which have been pretreated with oestrogen. The study described here was performed in order to analyse the effects of Sandostatin on prolactin secretion and pituitary hyperplasia after chronic oestrogen stimulation, and simultaneously to validate the use of NMR-imaging as a method for repeated *in vivo* monitoring of pituitary size.

Male rats received 10 mg β-oestradiol-3-benzoate in a silastic implant: 61 days later, prolactin levels had increased more than 20-fold and pituitary size more than 3-fold. Alzet minipumps were implanted and 0.1, 1.0, and 10 µg/kg/h Sandostatin were infused for a further 4 weeks. The lowest dose had only a slight and transient effect on prolactin secretion and on pituitary size. The 1 µg/kg/h dose inhibited prolactin secretion by 50% during the whole experimental period and by day 28 had reduced pituitary size by almost 30%. The highest dose was only slightly more effective on both parameters. Growth hormone (GH) secretion was inhibited dose-dependently 1 day after starting infusion of Sandostatin. With 0.1 and 1 µg/kg/h the results were similar to those described for prolactin secretion, but after 10 µg/kg/h, an escape phenomenon was observed.

At the end of the experiment and after a final NMR-imaging, the animals were killed and the pituitaries were weighed. The correlation between imaging estimates and measured weight was excellent ($r = 0.96$)

These experiments demonstrate that a) Sandostatin inhibits prolactin secretion and reduces pituitary weight after hyperplasia induced by chronic oestrogen pretreatment, b) pituitary shrinkage is not dependent on complete suppression of GH secretion, and c) NMR-imaging is an excellent and valid tool to continuously monitor pituitary size.

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EFFECT OF CONTINUOUS IN VITRO EXPOSURE TO ESTRADIOL ON CELL PROLIFERATION IN CANINE MAMMARY TUMORS.

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We have studied the "in vitro" proliferative effect of estradiol (E_2) in canine mammary tumors. Ten tumors were examined for thymidine labeling indices (LI) and eight of them for estradiol (ER) and progesterone (PgR) receptors concentrations. Mammary tumor pieces (± 1 mm^3) were incubated in minimum essential medium (MEM) supplemented with either saline (controls, group A) or saline plus $1.7.10^{-9}$M E_2 (group B). Incubation was carried out for 6, 12, 24, 36, 48 or 72 hours. One hour before histological fixation, ^{3}H-Thymidine (^{3}H-TdR) was added at a concentration of 2 µCi/ml. After incubation, the tumor tissue was fixed, cut and processed for autoradiography. LI were assessed on 3000 cell nuclei scored on ten tumor sections per experimental condition. Seven tumors were ER and PgR positive (range respectively: 14-39 and 4-96 fmols/mg proteins) and one tumor was ER and PgR negative. The mean LI values obtained for the control group (A) and the E_2 stimulated group (B) were: after 12 hrs: 0.4 ± 0.1% (A) vs 2.1 ± 0.4% : $P<0.001$ (B); after 24 hrs: 0.7 ± 0.3%(A) vs 2.1 ± 0.6%: $P<0.01$ (B). In all ER(+) PgR(+) tumors, a very significant increase (Fischer Test) of LI was observed, which lasted for 48 to 72 hrs. In the ER(-) PgR(-) tumor, a nearly significant very low increase was also observed ($P<0.05$) after 6 hrs or 12 hrs incubation only. The Spearman and Kendall rank correlation test between LI measured at 12 hrs after E_2 stimulations and ER and PgR concentrations gave a significative correlation ($r=0,7$; $P<0.05$). These results indicate that proliferation of the canine mammary tumors can be influenced by "in vitro" continuous exposure to E_2

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EFFECT OF TAMOXIFEN ON THE CELL KINETICS OF THE T61 HUMAN BREAST CARCINOMA GROWN IN NUDE MICE

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Conflicting results have been reported on the effect of tamoxifen on the cell kinetics of human breast cancer grown in vitro (Osborne et al., Cancer Res. 43, 3583, 1983) and in nude mice (Brünner et al., Eur. J. Cancer 21, 1349, 1985). In order to elucidate the cell kinetic effect of tamoxifen on xenografted T61 tumors the technique of labelled mitoses (PLM) was used to investigate untreated and tamoxifen-treated tumors. Tamoxifen resulted in a cessation of the tumor growth without tumor shrinkage. However, the PLM results showed no significant differences between treated and untreated tumors. Hence, the results indicate that the growth inhibitory effect of tamoxifen was only due to an increase in the cell loss. These data are in agreement with previous results obtained with the use of flow cytometric DNA analysis, and thus suggest that tamoxifen has no application as a synchronising agent in combination therapy with cell cycle phase specific drugs in tumors with a response similar to the T61.

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CYTOXAN, EPIRUBICIN, METHOTREXATE AND 5-FLUOROURACIL WITH HORMONAL SYNCHRONIZATION (TAMOXIFEN→PREMARIN) IN ADVANCED BREAST CANCER: A PHASE II STUDY.

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Thirty-three postmenopausal women with metastatic breast cancer were treated with the following regimen closely related to Lippman's experience: cytoxan 500 mg/m² iv day 1, epirubicin 30 mg/m²iv day 1, tamoxifen 10 mg/m²iv days 2 to 6, Premarin 0.625 mg/m²po q12hx3 doses day 7, methotrexate 300 mg/m²iv day 8, 5 FU 500 mg/m²iv day 9, Leucovorin 10 mg/m²po q6hx6 doses beginning 24 hrs after methotrexate. Up to now 31/33 consecutive patients (pts) are fully evaluable. Their main characteristics are: mean age 53.4 yrs (27-72), mean disease-free interval 27 months (0-87), mean PS 2 (1-4) (ECOG), prior chemotherapy (CT) 21/31, prior hormonal therapy (HT) 13/31. Estrogen receptor assay was positive in 12 pts, negative in 7 and unknown in 12. Predominant metastatic sites were: soft tissue in 3, visceral in 15 and bone in 13. Overall response rate was 25% (1CR+7PR) with a 95% confidence interval between 10 and 40%. Among the 10 previously CT untreated pts, 5 responded (50%) vs. 3 out of 21 (14%) in the pretreated group (p 0.6). Five out of 12 pts with ER+tumor responded (41%) vs. 1 out of 7 (14%) with ER-tumor (p 0.6). Two out of 12 pts with ER-unknown tumor achieved a PR (16%). Toxicity was moderate, including two episodes of life-threatening leucopenia: 4 pts experienced grade III haematological toxicity (2 for leucopenia and 2 for thrombocytopenia). Grade III-IV oral mucositis was seen in 10 pts. Our results in this series of poor-prognosis metastatic breast cancer pts, mainly pretreated, suggest that this regimen had limited but definite activity and deserves further evaluations.