61

SOMATOSTATIN RECEPTOR IMAGING WITH ^{123}I-Tyr^3-OCTREOTIDE.

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^{123}I-Tyr^3-octreotide (10-15 mC) was injected intravenously in patients who were suspected to have Somatostatin (S)-receptor positive tumors and planar and ECT images were obtained with a gamma camera. This scanning procedure revealed the localization of the primary tumor and/or its previously unknown metastases in 7 of 9 patients with endocrine pancreatic tumors. There was a close relationship between a positive scan, the presence of S-receptors in vitro, and the in vivo and in vitro sensitivity of hormone secretion to octreotide. Two insulinomas which could not be detected in vivo, were subsequently demonstrated to be avoid of S-analog receptors. In 12 of 13 patients with metastatic carcinoids the primary and metastatic tumors could be visualized, while these 12 patients were subsequently shown to respond well to therapy with octreotide. Paragangliomas, small cell lung cancers, neuroblastomas, astrocytomas, hormone secreting pituitary tumors and a minority breast cancers could also be visualized. This is a easy, harmless and cheap diagnostic method in the detection of S receptor positive cancers in man. It helps in the localization of multiple and/or metastatic tumors, predicts the successful control of hormonal hypersecretion by octreotide and seems of prognostic value for certain types of tumors.

62

Inhibition of prolactin and growth hormone secretion in the treatment of breast and prostate cancer. A. Manni, A. Boucher, L. Demers, H. Harvey, A. Lipton, M. Simmonds, M. Bartholomew. Depts of Med, Path and Ctr for Biostat. Epidemiol, the MS Hershey Med Ctr, PA State U., Hershey, PA 17033.

Suppression of lactogenic activity with the combined use of the newly developed somatostatin analogs (SMS) and dopaminergic drugs may induce regression of hormone-dependent tumors, such as breast and prostate cancer. In a phase I clinical trial, we administered SMS 201-995 (100-200 µg s.c. BID) and bromocriptine (2.5 mg p.o. BID) to 10 heavily pre-treated postmenopausal women with advanced breast cancer. During treatment, growth hormone levels following provocative testing were suppressed in 7/9 patients, while basal somatomedin-C decreased in 6/9. Prolactin secretion was almost totally abolished in 8/9 patients. Circulating levels of FSH, LH, E_1, E_1-S, E_2, T_4, T_3 RU and cortisol were not affected. Nausea occurred in 3 patients, requiring discontinuation of treatment in one. One patient experienced disease stabilization lasting 7 months. SMS analogs, particularly when combined with LHRH agonists, induce regression of experimental prostate cancer. The efficacy of this treatment in humans, however, has not yet been demonstrated. In addition to suppression of lactogenic hormones, SMS analogs may have direct antitumor effects through inhibition of growth factor mediated signal transduction.

63

GROWTH FACTOR-RECEPTOR PATHWAY INTERFERING TREATMENT BY SOMATOSTATIN ANALOGS AND SURAMIN: (PRE)CLINICAL STUDIES

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Blocking growth factor (GF) mediated pathways is a new strategy in the treatment of cancer. Somatostatin analogs (SMS-As) can inhibit hormone and GF secretion, while suramin can block the binding of several GFs to their receptors. SMS-As can cause direct growth inhibitory effects after binding to the somatostatin receptor (SMS-R). We tested the efficacy and endocrine effects of SMS-As (sandostatin, RC-160, CGP 15-425) and suramin in several tumor models and various cancer patients. SMS-A treatment caused growth inhibition of breast cancer cells (MCF-7) in-vitro, and of rat transplantable pancreatic (50-70% inhibition) and prostatic Dunning tumors (12% inhibition). No inhibition of DMBA-induced rat mammary tumors or a transplantable colon tumor or a rhabdomyosarcoma. In 34 patients with metastatic pancreatic or gastrointestinal tumors chronic sandostatin treatment caused stable disease in 27% of the patients, but no objective remission. SMS-Rs were found in the responding rat tumors and in 20% of human breast cancer specimens (J.C. Reubi), but not in rat DMBA-mammary tumors or in 10 human pancreatic tumors. Suramin caused dose-dependent growth inhibition of human breast cancer cells in-vitro and slight growth inhibition in rat pancreatic tumors (plasma levels up to 150µg/ml). In a preliminary clinical study of 11 patients with various tumors we observed significant haematological, biochemical, endocrine and side-effects, but no objective remission (peak plasma suramin levels 270-330µg/ml). In conclusion: SMS-As and suramin can cause growth inhibition in several types of tumor cells. Supported by The Dutch Cancer Society (RRTI 85-15), Sandoz, Ciba Geigy, and Bristol Meyers.

65

MANIPULATION OF CELL CYCLE KINETICS; INFLUENCE ON UPTAKE, CELLULAR DISTRIBUTION AND CYTOTOXICITY OF DOXORUBICIN

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We have studied the effects of estradiol on cellular uptake, cellular distribution, and cytotoxicity of doxorubicin (DOX) on two human breast cancer cell lines (MCF-7: ER+, EVSA-T: ER-). In medium, lacking phenol red and supplemented with 4.5% (MCF-7) and 2.5% (EVSA-T) dextran-coated charcoal-treated foetal calf serum, estradiol (1 nM) was added after preculture for 48 h. Following stimulation for 24 h the percentage of cells in the S-phase (determined by PI/anti-BrdUrd FITC fluorescence) increased maximally 10-fold in MCF-7 cell line, after a lag period of 6-12 h. In EVSA-T cells no stimulation with estradiol was observed.
The effects of estradiol pretreatment on the cellular uptake of doxorubicin (DOX) by MCF-7 and EVSA-T cells was measured by HPLC and flow cytometry, and the DOX distribution in MCF-7 cells was investigated by fluorescent microscopy. Growth curves were used to establish differences in survival due to this combined treatment. In both cell lines pretreatment with estradiol (15-21 h) had overall no significant effect on the uptake of 0.04-3.0 uM DOX administered for 0.5-23 h. But in the ER+ MCF-7 cells estradiol pretreatment resulted in a more impaired cell growth or better cell kill in 8 out of 9 exp. (44±19%), compared to unstimulated controls. After a 3 h incubation with 185 nM DOX there was nuclear fluorescence, augmenting with increasing DOX concentrations and incubation time, and which was unaffected by estradiol. Weak cytoplasmatic fluorescence became apparent only after prolonged incubation time and higher DOX concentrations.In conclusion: estradiol pretreatment of ER+ breast cancer cells may cause an augmented cytotoxic effect of DOX, not mediated by increased uptake of the drug, but probably via influence of cell kinetics.
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