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Effect of Sandostatin on the basal and gastrin stimulated growth of gastrointestinal (G.I.) cancer cells

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Somatostatin has been shown to reduce G.I. tumour growth which may be direct via receptor binding or indirect via the effect on gastrin and other growth factors.

We have analysed the effect of the long acting somatostatin analogue, Sandostatin, on the basal and gastrin stimulated growth of the following somatostatin and gastrin receptor positive tumour cell lines: AR42J, rat pancreatic; LoVo, human colon; MKN45, human gastric; MKN45G clonal variant of MKN45 with intracellular gastrin immunoreactivity.

The basal in vitro growth of the first 3 cell lines was unaffected by Sandostatin (3.7×10^{-8} and 3.7×10^{-7}M) as measured by ^{75}Selenomethionine uptake, yet the basal growth of MKN45G was modestly inhibited (80% of untreated control). In vivo, the growth of MKN45 xenografts was unaffected by continuously administered Sandostatin (240 and 25μg/kg, 14 day osmotic mini pumps) whereas MKN45G showed inhibited growth ($p<0.001$, after 13 days therapy).

AR42J and LoVo were stimulated mitogenically in vitro by physiological gastrin concentrations (10^{-11} to 10^{-9}M) and in all experiments Sandostatin (3.7×10^{-8} and 3.7×10^{-7}M) reduced this stimulated growth.

In addition, a high proportion of freshly prepared primary G.I. tumour cells have been found to respond mitogenically to G17 and it was shown that 5/8 colorectal and 3/5 gastric tumour cells had a significantly reduced gastrin response when co-treated with Sandostatin.

Sandostatin may play a role in endocrine therapy of G.I. tumours.

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MODIFIED pS2 EXPRESSION IN HUMAN STOMACH CARCINOMA

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The expression of the human pS2 gene, coding for a secreted peptide of unknown function and isolated from the breast carcinoma cell line MCF7, was shown to be under estrogen control. Surprisingly, it was found active in normal stomach surface epithelial cells where its activity proved to be estrogen-independent. We now investigated pS2 expression in 17 stomach carcinomas in comparison to their matrix tissue. All carcinoma samples were positive when tested at the RNA (Northern blots) and protein level (immunostaining), however, pS2 expression was, in general, weaker in tumor cells than in corresponding healthy tissue. Among the tumors, the diffuse type (according to classification by Laurin) showed the strongest immunostaining. Next to this observed down-regulation of pS2 some carcinoma samples displayed RNA bands of altered size. Such aberrant transcripts are likely explained by modification of the processing pathway. The function of regular and changed transcripts still awaits elucidation.

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HORMONAL TREATMENT OF ADVANCED PANCREATIC CANCER WITH LH-RH ANALOGUE.

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Recently estrogen and androgen receptors have been demonstrated in normal and malignant pancreatic tissue. It was therefore proposed that endocrine manipulation may be valuable in the treatment of this malignancy. Case reports of objective responses to LH-RH analogues have also been published (Lancet, 1986). In this study we report the results of the treatment of unresectable pancreatic cancer with a LH-RH analogue, goserelin. 33 patients with histologically proven pancreatic adenocarcinoma entered in the study and randomized in 2 groups: group A (15 patients) treated with goserelin (Zoladex, ICI Pharma, Milan, Italy) 3.6 mg s.c. every 4 weeks and group B of 18 untreated patients. Patients were reviewed monthly for clinical examination, routine laboratory tests, Ca19-9 serum levels, and every 3 months chest x-ray, abdominal U.S. and /or CT were performed. LH secretion was successfully suppresed by goserelin, and serum testosteron fell dramatically in males. Survival time from diagnosis was evaluted statistically in both groups by Mantel- Cox, Tarone and generalized Wilcoxon tests. No objective response to treatment was demonstrated, either complete or partial. No sustained improvement in performance status and decrease of Ca 19-9 serum levels were observed despite theraphy. Three patients in group A and 3 in group B had stable disease; 2 patients in both groups survived > 1 year. Survival was not statistically different in 2 groups ($p = 0.21$). Median survival time was 7 months for group A and 4 months for group B. No toxicity due to LH -RH agonist administration was seen. This study suggest that LH-RH analogues are unlikely to have a major influence in survival of patients with pancreatic cancer.

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MELATONIN AS A TREATMENT OF HUMAN ADVANCED MALIGNANCIES: A PHASE II STUDY. Farina G.°,Scaglione F.*,Dugnani S.*,Ferrara F.*,Maccarinelli G.*,Perrone S.°,Tomirotti M.°,Fraschini F.*,Scanni A.° - °Dep.Med.Oncology and Chemoth.-Fatebenefratelli Opht.Milan - *Dep.of Pharmacology,Chemoth and Toxicol.Univ.of Milan. Italy.

The present study was undertaken to evaluate the antineoplastic activity and the tolerability of Melatonin in pts. bearing advanced malignancies resistant to the conventional therapies. 14 pts. (6 ♀ and 8 ♂),mean age 61,3 (range 33-77)were included in this investigation:9 had colorectum cancer, 2 breast cancer, 2 stomach cancer, 1 lung adenocarcinoma. In these pts. intramuscolar Melatonin was given (20 mg /day at 3 p.m.)for at least 2 months, followed by oral administration (10 mg/day) in case of response or stabilization of the disease. All required examinations were performed in order to evaluate the response. Besides, the natural killer cell (NK) activity and the phagocyte activity were regularly assayed on days 0,15,30,45,60 after the beginning of treatment (data in processing). The evaluable pts. were 12; we achieved 11 PROs and 1 RP> 50% (4+ mos). The inevaluable ones were 2: 1 went off protocol because of toxicity (nausea, vomiting, severe asthenia since the beginning of treatment) and 1 was lost to follow-up. We also observed the following individual effects: improvement in PS (3/14); increase of appetite (4/14); reduction of asthenia (6/14); improvement in morale (3/14). 1 pt. showed severe asthenia following the end of treatment. The pt. showing a PR (basal NK activity= 14%; after 15 days= 21%; 30 days= 26,7%; 45 days= 20,6%; 60 days=27%) was the only one contemporarily treated with slow-relmease morphine (120 mg. twice per day). This result might be related to a favourable interaction between opioids and Melatonin (Cancer 62: 494-499, 1988).