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A COMPARISON OF THREE LOADING REGIMENS OF SURAMIN IN CANCER PATIENTS.

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Suramin is a novel antitumor agent which has been shown to be a growth factor antagonist and which has produced responses in patients refractory to other forms of cancer therapy. The probability of response correlates with serum levels >200 mg/L, however the optimum manner of obtaining and maintaining these levels has not been determined. Three loading regimens have been compared for their ability to produce the proposed therapeutic serum levels of suramin. Regime A was a continuous infusion of 350 mg/m^2/day of suramin dissolved in 2L 0.9% NaCl given for 10 to 14 days. In regime B, suramin 1 to 1.5 gm dissolved in 1L 0.9% NaCl and administered over 6 hours was given weekly for six weeks on an outpatient basis. Whilst in regime C 600 mg/m^2/day of suramin was given daily as a six hour infusion for 10 days. Suramin levels were measured daily in regimen A & C and weekly for regime B.

Three patients were treated according to schema A. At the end of therapy the levels were 160 to 234 mg/L. Six patients received regime B but 2 did not complete therapy because of WHO grade II stomatitis and grade III leukopenia after 4 weeks. With cumulative suramin doses of between 4 & 8.5 gm serum levels were between 43 & 184 mg/L. Regime C gave suramin levels of 259 to 450 in 7 to 9 days. These levels declined within 1 week to <250 mg/L.

All patients receiving suramin on a daily basis developed ankle oedema and serum albumin levels fell from 31.6±4.7 to 24±5.3 g/L. Otherwise toxicities between A, B & C were not different.

Regime B was discarded because serum levels increased slowly and several patients developed progressive disease before attaining levels >200 mg/L. C appeared superior to A because serum levels > 200 mg/L were obtained in a shorter period of time without undue toxicity, thus minimising hospital stay.

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PHASE I/II STUDY OF SURAMIN IN HORMONE RESISTANT METASTATIC PROSTATE CANCER.

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The results of chemotherapy in hormone resistant metastatic prostate cancer are poor. Recently it has been reported the antihelmintic agent and growth factor antagonist suramin inhibits the growth of prostate cancer cells in vitro, and induced responses in several patients treated with the drug. We have, therefore initiated a phase I/II study of suramin in this patient group.

Nine patients have been entered. All had documented progression on hormone therapy and four of them had also been treated with Mitomycin C. Six patients were given 1 to 1.5 gm of suramin weekly, 3 received a loading course of 600 mg/m^2/day for 7-8 days and maintenance with 600 mg/m^2/week. Suramin was delivered in 1L NaCl 0.9% given over 6 hours in order to improve tolerance to the therapy. Treatment was withheld if suramin levels were >250 mg/L or ≥ WHO grade II toxicity was observed.

Three patients responded with a reduction in prostate specific antigen levels of >90% and in one subject there was a >50% reduction in size of a measurable supraclavicular lymph node. Four patients, including all responders are alive 8+ to 29+ weeks from the start of therapy. Five patients died after 7 to 29 weeks. Death was due to progressive disease in four and one was regarded as a toxic death. This patient died 7 weeks from the start of suramin therapy of severe diarrhoea and shock. Other toxicities (number of patients) included adrenal insufficiency (4), changes in taste (4), stomatitis (2), diarrhoea (2), skin rash, vortex keratopathy, prolonged APTT & leukopenia (1 each). Suramin induces responses in prostate cancer but patients may require corticosteroid replacement therapy.

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REGULATION OF EPIDERMAL GROWTH FACTOR (EGF) RECEPTOR IN NEOPLASTIC AND NON-NEOPLASTIC PROSTATIC CELL LINES.

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In previous studies we have shown that EGF is a potent mitogen in cultures of both normal (1) and neoplastic prostatic cells and that EGF receptors are present at varying concentrations in prostatic tumours (2). Using serum free conditions we have now studied the effects culture cell density, steroid depleted foetal calf serum, androgens, and retinoic acid on EGF receptor expression in a non-neoplastic canine prostatic cell line (CAPE) and in two prostatic tumour cell lines of canine (CPA) and human origin (LNCaP). Under the culture conditions used our results suggest that high affinity (Kd ≈ 0.2-0.5 nM) receptor expression is markedly downregulated in the non-neoplastic cell type at high cell densities. Our data also indicates that both EGF receptor content and EGF receptor mRNA expression is downregulated by serum and upregulated by retinoic acid in all cell lines studied. The studies partially confirm the findings of others in respect of receptor augmentation in response to androgen in one cell line (LNCaP) but also suggest suppression of receptor content in the non-neoplastic cell line in the presence of these steroids during confluent growth.

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PROSTATE CANCER AND EPIDERMAL GROWTH FACTOR RECEPTORS

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There are distinct zones within the prostate and the majority of cancers arise in the peripheral zone, whereas benign prostatic hyperplasia (BPH) originates in the periurethral transition zone. This study aimed to compare epidermal growth factor receptor (EGFR) binding in these zones, and between BPH and prostatic cancer.

Specimens were taken from ultrasound guided biopsy in patients with BPH (n=25), carcinoma (n=12) and controls (n=12). EGFR binding was measured with a ^{125}Iodine radio labelled EGF, single dose binding assay, and full Scatchard analysis when sufficient tissue was obtained at subsequent operation.

In the patients with BPH a significantly greater concentration of specific EGF binding was found in the transitional zone (75.7 +/-5.14 fmol/mg protein) compared to the peripheral zone (19.4 +/-2.3), and the biphasic Scatchard plots suggested two different receptor binding affinities in BPH tissue. There was increased specific binding in the prostatic carcinomas (137.9 +/-28.2), compared to the controls (44.1 +/-6.3), this was associated with loss of the low affinity binding site. In the control group the difference between the two zones was less marked.

These results suggest that EGF is involved not only in the pathogenesis of BPH but also in the proliferation of prostatic cancer cells. Furthermore the developing imbalance of high and low affinity sites may be associated with tumour dedifferentiation.