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ANDROGEN PRIMING AND RESPONSE TO CHEMOTHERAPY IN ADVANCED PROSTATE CANCER. R. Santen, A. Manni, A. Boucher, A. Lipton, H. Harvey, D. White, M. Simmonds, R. Gordon, T. Rohner, J. Drago, J. Wettlaufer and L. Glode. Depts of Medicine and Surgery, The M.S. Hershey Med. Ctr. The PA State Univ., Hershey, PA and Univ. of Colorado Health Sciences Ctr., DENVER CO.

Sixty-seven orchiectomized men with progressive stage D2 prostate cancer have been entered in a controlled trial to test whether transient androgen stimulation of tumor growth enhances the efficacy of cytotoxic drugs. Median duration of follow-up is 24 months. All patients are treated with aminoglutethimide (1g/day) and hydrocortisone (40mg/day) to lower adrenal androgen secretion, plus intravenous cytoxan (500mg/M^2), adriamycin (50mg/M^2) and 5-fluorouracil (500mg/M^2) every 3 weeks. Patients in the stimulation arm (n=34) receive, in addition, fluoxymesterone (5mg bid) for 3 days before and on the day of chemotherapy. The 2 groups are comparable with respect to age, performance status, baseline hematocrit, time from castration, extent of metastatic disease and previous therapy. Response rate (objective remission + stabilization of disease) was higher in the stimulation than in the control arm (85% vs 72%, $p < 0.05$) when the analysis was restricted to evaluable patients (20 in the stimulation arm and 28 in the control group). No difference has been observed in median duration of response (9 months in both groups) or survival (13 months : stimulation arm ; 16 months, control arm). Our data suggest that androgen priming may enhance the response rate to chemotherapy. The large proportion of hormone-independent cells present limit response duration and survival.

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NUCLEAR THYROID HORMONE RECEPTORS IN HUMAN TUMORS OF THE CENTRAL NERVOUS SYSTEM

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The role of thyroid hormones in the incidence and pathogenesis of human cancer remains a controversial subject. Subpopulations of cells containing nuclear triiodothyronine (T_3) receptors have been identified in developing and adult rat brain, suggesting that, at least some of the effects of the thyroid hormones on the central nervous system (CNS) might result from a direct action of T_3 at the cellular level.

We have studied the T_3-binding capacity of nuclei isolated from individual samples of human cerebral tumors. The nuclear suspension, treated with 0.5% Triton X-100, was incubated with increasing concentrations of $^{125}I_1T_3$. Only high affinity T3-binding sites (K_a = 1-4 x 10^9 M^{-1}) were considered for Scatchard analysis. In two cellular medulloblastomas, the T_3 receptor level (C_{max} = 262 ± 5 fmol/mg DNA) was slightly higher than the value reported for the rat cerebellum (C_{max} = 120 fmol/mg DNA). Similar concentrations of T_3 receptors were found in tumors of neuroglial origin : astrocytomas grade 1 and 2 (n = 4 ; C_{max} = 212 ± 26 fmol/mg DNA) ; glioblastomas, astrocytomas grade 3 and 4 (n = 6 ; C_{max} = 346 ± 123 fmol/mg DNA). The variable T_3-binding capacity (range : 182-555 fmol/mg DNA) may be due to the degree of dedifferentiation of the tumor and to the heterogenicity of the cell population of human malignant gliomas. In mature rat brain, T_3 receptors are preferentially localized in neurons and hardly detectable in glial nuclei. The presence of significant amounts of T_3 receptors, even in higly malignant astrocytomas, indicates that CNS tumors remain potential targets of the thyroid hormones.

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ANDROGENS IN A TRANSPLANTABLE HUMAN PROSTATE CANCER LINE (PC-82): CORRELATION WITH PROLIFERATION.

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The hormone-dependent human prostatic tumor line, PC-82, which is permanently transplantable in nude mice, was used as a model to study the effects of hormonal manipulation on tissue levels of androgens and on the proliferative activity of the tumor. Endogenous levels of testosterone (T) and 5α-dihydrotestosterone (DHT) were measured in whole tissue homogenates by radioimmunoassay. The proliferative activity of the tumor tissue was estimated in frozen tissue sections using a monoclonal antibody, Ki-67, directed against a cell proliferation-associated nuclear antigen (PaNA). In PC-82 tumor tissue grown in intact male mice mean levels of T and DHT were 22 and 18 pmol/g tissue respectively. Tissue grown in mice receiving a Silastic T-implant contained similar levels of T and DHT, with a smaller inter-individual variation than found in intact mice. Androgen withdrawal in PC-82 bearing T-implanted female mice resulted in a decline of the concentration of T and in a more gradual decrease of DHT in the tumor tissue. After 10 days T and DHT concentrations were below 0.5 pmol/g tissue and the expression of the PaNA had decreased from about 20% in control tissue to 0.2% in tissue grown in mice depleted of androgen. In these androgen depleted tissues control levels of T and DHT were restored within two days after reimplantation of T. This androgen repletion resulted in a rise of the tumor cell proliferative fraction to 20% within four days. The present results with the PC-82 tumor model yield valuable information on the effects of hormonal manipulation on steroid levels in human prostatic carcinoma tissue. The Ki-67 antibody provides a reliable method for estimation of the proliferative fraction of hormone-responsive cancer tissue.