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7.031

Novel biologically active palladium (II) complexes of some β-carbolines alkaloids as reverse trans-criptase inhibitors (In Vitro)

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The biological activity of some Palladium(II complexes of some β- carboline (harmaline , harmalol , harmine , harmane) and the free a lkaloids were examined for activity in inhibiting reverse- transcriptase , the target enzyme of HIV-Virus .

Of the compounds tested , only one complex showed an activity similar to that for Foscarnet (PFA) . The IC_{50} was found to be 11-17 µg/ml.

The in vitro studies on this complex showed no toxicity on both MRC-5 and / or O-Hela cells at 25 µg/ml. Further , the mutagenic studies using Ames Test confirm the above results .

7.032

PROTRACTED INFUSION (PI) OF 5-FU+FA IN ADVANCED COLORECTAL CANCER

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The administration of 5-FU in colorectal cancer by PI improves the response rates compared with traditional bolus schedule. Between march 1986 until march 1991, 28 patients (pts) with median age 54 years (range 40-74) with histologically confirmed adenocarcinoma, in progression after chemotherapy (bolus) have been selected. All pts showed misurable disease and ingravescent symptomatology secondary to the cancer (fever, abdominal pain, anorexia and subocclusion). All the pts have metastatic disease at liver and/or peritoneum and lung. In each pts a Porth-A-Cath connected with a pump delivery sistem (Deltec Caddl PHARMACIA), in subclavian vein, was implanted. This trial include 5-FU 100-150 mg/mq/die in PI, Folinic Acid (FA) 70-80 mg/mq/die/os and Allopurinol 300 mg/mq/die/os. The drugs until progression of disease were delivered, mean 9 months (range 5-16). The results of these study show that 20% about of pts have a clinical response more than 50% and in all the pts a complete remission of pain was obtained (mean 9 months, range 5-12). The mean of overall survival was 11 months (range 6-16). The side effects include mucositis, nausea, vomiting, diarrhoea and mielocardiotoxicity, in 2 pts erythodysesthesia sindrome were observed. In conclusion in to pts with colorectal cancer, in progression of disease after bolus therapy , it is possible geted with PI remission of secondary symptomatology to the cancer and improve the pts quality of life.

7.033

EFFECTS OF IL-6, ALONE AND IN COMBINATION WITH CHEMOTHERAPEUTIC AGENTS OR RADIOTHERAPY, ON THE GROWTH OF HUMAN TUMOR XENOGRAFTS

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The therapeutic effects of recombinant human IL-6 (rhIL-6), alone and in combination with Adriamycin or 5-FU or radiation, were studied in nude mice bearing subcutaneous (sc) xenografts of human carcinoma cells - either mammary (MDA 468) or colon (KL-C2, CCL 227, CCL 228). The response of human tumors growing sc on nude mice to intraperitoneal (ip) treatment with rhIL-6 was tested first. RhIL-6 caused a significant growth delay of the MDA 468 and the KL-C2 tumors. Next we studied the growth inhibitory effects of rhIL-6 in combination with Adriamycin on the mammary xenografts, and in combination with 5-FU on the colon carcinoma xenografts. Adriamycine and 5-FU were administered intravenously (iv) as a single dose via the lateral tail vein on day 1. RhIL-6 was subsequently administered ip from days 3-12. Adriamycine and 5-FU alone led to significant growth delays. The growth delay in the mammary carcinoma line MDA 468 due to the chemotherapy was not changed significantly by the subsequent course of IL-6. However, in two of the three colon carcinoma lines (KL-C2 and CCL 227) an encreased tumoreductive effect of IL-6 in combination with 5-FU could be observed. Irradiation of the sc growing MDA 468 mammary tumors led to an extensive growth delay. Combined treatment with IL-6 and irradiation did not led to an increased tumoreductive effect in this mammary xenograft. We conclude that the combination of certain chemotherapeutic agents with IL-6 appears to be an useful approach for increasing the efficacy of cancer treatment in some types of carcinoma entities.

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7.034

SYNERGISTIC ENHANCEMENT OF MITOXANTRONE-EFFECT BY TUMOR NECROSIS FACTOR (TNF).

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A wide range of TNF concentrations (from 0.01 to 10.000 U/ml) was tested in seven human epithelial ovarian cancer cell lines. TNF was cytotoxic in four cell lines (A2780, A2774, SW626, Pa1) while three cell lines (IGROV-1, SKOV3, Me 180) were marginally sensitive to its activity. TNF also markedly enhanced the Mitoxantrone-cytotoxicity in six cell lines, without affecting Mitoxantrone-accumulation. When cells were incubated with Mitoxantrone+TNF, increased number of DNA single-strand breaks were produced. TNF alone did not induce DNA strand-breaks. This study suggests that the lethality to ovarian cancer cell lines from Mitoxantrone treatment was increased by TNF "in vitro". We suggest that TNF may be a useful adjuvant to Mitoxantrone and that this result serves as a "rationale" for clinical trials employing the combination of TNF and Mitoxantrone in patients with advanced ovarian carcinoma, relapsing after a standard chemotherapy. A phase I study of this combination, give i.p. in patients with carcinoma and ascites, refractory to conventional modes of therapy, is now in progress. (AIRC "BRM" and KNOLL).

7.035

PRODUCTION AND CHARACTERIZATION OF BISPECIFIC MONOCLONAL ANTIBODIES (BsMAbs) RECOGNIZING THE EGF-RECEPTOR (EGF-R) AND DOXORUBICIN (DXR).

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In order to specifically target DXR on tumor cells, BsMAbs (DOXER2) were produced by fusing two hybridomas which produced MAbs against DXR(MAD11) and EGF-R (MINT5) respectively. The DOXER2 was found to inhibit the DXR-induced cytotoxicity on EGF-R negative cells (MEWO) or on cells with normal expression of EGF-R (HT-29) showing a similar antidotal activity as the parental MAD11 MAb alone. On the contrary, on cells with EGF-R overexpression (A431) the DXR-induced cytotoxicity was inhibited by the MAD11 parental MAb but not by the DOXER2 bifunctional MAb. The results indicate that a specific cytotoxic activity can be obtained on relevant EGF-R overexpressing cells by the complex DOXER2/DXR.

7.036

B-CLL influence on T cell functions.

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Previously we have shown that CLL B cells are capable of supressive factor (SBF) production that inhibits B cell proliferation and differentiation both of healthy donor and leukemia patient B cells. The given investigation revealed the SBF influence upon T cell functions It has been shown that partially purified SBF in a dose-dependent manner inhibits up to 95% of T cell proliferation level, up to 50% of IL-2 production and fully abrogates responsiveness of T cell blasts to IL-2. Besides of T cell depression SBF decreases NK cell activity. Except of SBF action on lymphocytes it changes L929 cell line growth. The SBF nature investigation revealed that its m.w. is about 14 kD. Taken together these data allowed us to suggest the possible similarity of SBF and transforming growth factor β (TGF-β).