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UKRAIN INDUCED BIMODAL CELL DEATH IN WILD-TYPE AND MULTIDRUG RESISTANT CEM LEUKEMIA CELLS

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Progress has been made in the treatment of cancer diseases, such as malignant lymphoma, acute leukemia and certain solid tumors. Unfortunately, the majority of patients who had initially responded to chemotherapy will relapse and die of their disease. The failure to respond to subsequent chemotherapies is thought to be primarily due to the development of multidrug resistance (MDR). The principle mechanism which is resposible for the induction of multidrug resistance is due to an over-expression of the MDR-1 gene and its product P-glycoprotein (Pgp) on the tumor cells. Thus, from the clinical standpoint, it is of great importance to find therapeutic agents or treatment modalities that will overcome the MDR phenomenon.

The present studies were undertaken in order to determine whether the alkaloid derivative Ukrain (NSC 631570) and the PKC inhibiting alkaloid sanguinarine would overcome the MDR phenomenon in CEN-VLB-1000 cells in vitro. Results showed that these compounds - at a concentration of 2.0 to 32.0 M (serial dilutions) - were capable of inducing bimodal cell death with equal effectiveness in CEM leukemia wild type as well as in their MDR-VLB-1000 CEM counterparts. The latter MDR cell line expressed high levels of Pgp on ist cell surface membrane, thus demonstrating that Pgp does not confer resistance to Ukrain, and sanguinarine induced cell death or apoptosis.

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ACTIVATION OF IMMUNE EFFECTOR CELL CYTOLYTIC ACTIVITY BY THE ALKALOID DERIVATIVE UKRAIN (NSC631570)

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Purpose: To investigate the possible modulation of immune effector cells cytolytic activities by the alkaloid thiophosphoric acid derivative ukrain (NSC 631570).

Methods: The cytolytic activity of alloimmunized spleen lymphocytes and peritoneal macrophages (P&M) from tumor bearing animals were assayed *in vitro* by ^{51}Cr release assays in the presence of various concentrations of ukrain in the CML assays.

Results: The cytolytic activity of freshly isolated spleen lymphocytes from P815 (H-2^d) alloimmunized C57Bl/6 mice, which had no significant endogenous cytolytic activity, i.e. < 2.0% specific ^{51}Cr release, were found to increase their lytic activity to 65.0% in the presence of 1.2 μM of ukrain. The *in vitro* CML assays were carried out at E/T = 5:1 for 3.5 hrs.

The effects of ukrain on the cytolytic activity of peritoneal macrophages (PM) of Babl/c bearing syngeneic D1-DMBA-3 tumors, were also assayed *in vitro*. Results showed that ukrain at 2.5 μM activated the cytolytic activity of macrophages from 0% to 13.0% specific lysis of syngeneic tumor cells. Moreover, *in vivo* studies with Balb/c mice bearing syngeneic mammary adenocarcinomas showed that ukrain had a significant inhibition of tumor growth and progression.

Conclusions: In view of the *in vitro* data, where ukrain was found to activate the cytolytic activity of spleen lymphocytes as well as anergic macrophages obtained from mice bearing syngeneic tumors, indicates that this compound functions as a biologic response modifier (BRM). This conclusion is further supported by the finding that ukrain reduced significantly the growth rate of established mammary adenocarcinomas without any observable side effects.

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NEO-ADJUVANT CHEMO-(IMMUNO-) THERAPY OF ADVANCED HEAD AND NECK SQUAMOUS CELL CARCINOMA (HNSCC): A MULTICENTER PHASE III RANDOMIZED STUDY COMPARING CISPLATIN (CDDP) + 5-FU WITH CDDP + 5-FU + RECOMBINANT INTERLEUKIN 2 (rIL 2): PRELIMINARY RESULTS

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We designed an open, randomized phase III multicenter clinical trial to evaluate in neoadjuvant setting the clinical response and toxicity of the combination chemotherapy CDDP + 5-FU compared with the same combination plus s.c. rIL 2 in patients (pts) with advanced stage (III-IV) HNSCC. The study is still underway and only preliminary results are reported. From August 1995 to August 1996 25 pts (21 males and 4 females, mean age 54.76 years, range 38-72; PS ECOG 0-2, median 0; Stage III: 3 , Stage IV: 22 pts) have been enrolled in the study. Sites of primary were: oropharynx, 11; oral cavity, 4; hypopharynx, 4; larynx, 4; rhinopharynx, 1; undefined, 1. Treatment plan was: Arm A: CDDP 100 mg/m^2 on day 1, 5-FU 1000/mg/m^2 c.i. for 5 days and rIL 2 4.5 MIU s.c. on days 8-12, 15-19; Arm B: the same as Arm A without rIL 2, q 21 days for 3 cycles. 12 pts were randomized to Arm A and 13 to Arm B. 20 pts (9 for Arm A and 11 for Arm B) were evaluable for response and 25 (12 for Arm A and 13 for Arm B) for toxicity. 5 pts were not evaluable (3 therapy refusal, 1 early death due to broncopneumonitis and 1 toxic death, cardiac). There were 3 CR (33.33%) in Arm A and 2 (18.18%) in Arm B (p=0.062); 4 PR (44.44%) in Arm A, 6 (54.55%) in Arm B (p=0.198) with 7 OR (77.78%) in Arm A and 8 (72.73%) in Arm B (p=0.507); 2 SD (22.22%) in Arm A and 2 (18.18%) in Arm B, and 1 PD (9.09%) in Arm B. The received dose intensity of CDDP, 5-FU and rIL 2 was 84.93%, 84.73%, 88.13% for Arm A and 85.91%, 85.54%, for Arm B, respectively. Toxicity was generally acceptable. The main toxicities were cardiac grade IV (3.2%) and mucositis grade III (16.1%) in Arm A, hematological grade IV (7.9%) and grade III (5.3%) in Arm B. Both regimens are active. As for clinical response, no statistically significant difference was found between the two regimens.

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CHEMOIMMUNOTHERAPY WITH WEEKLY CISPLATIN AND ETOPOSIDE PLUS S.C. rIL-2 PLUS ORAL MEDROXYPROGESTERONE ACETATE (MPA) IN STAGE IIIB-IV NSCLC: PRELIMINARY RESULTS ON CLINICAL RESPONSE AND ON IMMUNOLOGIC ASSESSMENT

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Several cytokines, mainly interleukin (IL)-1, IL-2, IL-6 and tumor necrosis factor α (TNFα), are involved in the pathogenesis of anorexia/cachexia syndrome (ACS). In a previous study (Eur J Cancer, 1996 in press) we reported the effect of MPA on peripheral blood mononuclear cells (PBMC) from 10 cancer patients in advanced stage of disease. Our study provided evidence that MPA is able to hinder the activity of some cytokines, such as IL-1β, IL-6 and TNFα, by inhibiting their production and/or release. These experimental results prompted us to perform a phase II open clinical study of chemoimmunotherapy treatment of stage IIIB-IV inoperable NSCLC. The treatment plan consisted of cisplatin (50 mg/m^2 i.v.) and etoposide (100 mg/m^2 i.v.), combination administered on day 1 weekly for 6 cycles, plus recombinant Interleukin-2 (rIL-2) 1.8 MIU s.c. from day 2 to 7 weekly for 6 cycles, plus MPA 1000 mg/daily beginning 7 days before the chemotherapic treatment and during all treatment period (6 weeks). Twenty-three patients (M/F 19/4) with NSCLC were enrolled, 14 of whom (mean age 65.2 years, range 52-74; 6 stage IIIB, 8 stage IV) were evaluable for response and 17 for toxicity. There were 7% CR, 21% PR (OR 28%), 36% SD and 36% PD. The toxicity was acceptable: 3 patients were withdrawn from study for hematologic (Grade 3 anemia) and 1 for renal (Grade 2) toxicity. An immunological study carried out on 9 of these patients (2 stage IIIB and 7 stage IV) showed that the serum levels of cytokines IL-1β, IL-2, IL-6, IL-10, TNFα and IFNγ and the production in culture of the same cytokines by PHA-stimulated PBMC of patients did not change after treatment as compared to pretreatment values (only IL-2 production was significantly higher after treatment compared to values before treatment).

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