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ANTIMETASTATIC EFFECT OF TUMOR IRRADIATION AND r-IL-2 ON LUNG METASTASES IN THE RAT

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The effect of local tumor irradiation and multiple doses of recombinant IL-2(r-IL-2)given systemically on metastases formation in the lung of an anaplastic carcinoma(ACA) in the rat Y59 was studied. Animals received single therapies(local irradiation or r-IL-2)developed much less metastases than their respective control. However, in those receiving combination of local tumor radiotherapy and r-IL-2 either after or before irradiation, tumor metastases formation in the lung was more reduced. The number of leukocytes as well as lymphocytes in this treated group was elevated. Lymphocytes from animals receiving combined therapy were more tumorocidal than cells from control group as tested in ^{51}Cr releasing test. In conclusion, combined radioimmunotherapy used in this tumor system was more benefitial in controling metastasis formation than any therapy alone.

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EVALUATION OF THE PHAGOCYTOSIS DURING SUBCUTANEOUS RECOMBINANT IL-2 TREATMENT

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During cancer immunotherapy with Interleukin-2, both immunostimulatory and immunosuppressive events were observed. In this study we evaluated monocytic /macrophage phagocytosis in 10 patients with advanced cancer (metastatic renal cancer and malignant melanoma) during subcutaneous rIL-2 therapy; the indirect indices of monocitic/granulocyte activation as Neopterin (NPT), B2-microglobulin (B2M) and soluble IL-2 receptor (sIL-2R) were also evaluated. Moreover, we monitored the C3 and C4 fractions of Complement System. After rIL-2 injection we observed a decrease in the phagocytic response and a significant increase only in the NPT, B2M and sIL-2R serum levels (3, 2 and 6-fold respectively). It therefore appears that rIL-2 administration may induce the production of immature and functionally incompetent phagocytic cells. These findings may have important physiologic implications, because patients receiving rIL-2 therapy have been shown to have increased susceptibility to infection.
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THYMOPENTIN (SINTOMODULINA) PLUS CHEMOTHERAPY VS. CHEMOTHERAPY ALONE IN ADVANCED NEOPLASMS. PRELIMINARY DATA.

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104 pts. with advanced tumor were randomized to receive chemotherapy with or without thymopentin (50 mg twice a week for at least 3 months) from January 1992 to January 1993. The two groups were well balanced as regards the type of neoplasia, the chemotherapy regimen, the age and P.S.. The following parameters were compared in this study: the frequency of grade 4 myelotoxicity, the delivered dose intensity of chemotherapy, the frequency and severity of infectious events and the changes of the immunological parameters. To date 89 pts (46 treated and 43 controls) are evaluable for response (minimum two-month follow-up).Results:
A significantly lower number of pts. with infection (8 vs. 15; p=0.05) and higher number with CD4/CD8 or CD16+ increase (23 vs. 12; p=0.027) was observed in the TP-5 treated group. Also the N. of pts. who received 100% of the planned dose-intensity was higher in the treated group (37 vs. 28;p=0.08). Finally, grade 4 myelosuppression occurred in 6 pts. treated with TP-5 as compared to 11 controls (p=0.11) These data seem to suggest a definite effect of TP-5 in potentiating host immune response, preventing infections, and reducing the intensity and duration of myelosuppression.

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RANDOMIZED PHASE II STUDY LD-ARAC PLUS rhGM-CSF IN ADVANCED MYELODYSPLASIA

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Patients with myelodysplastic syndromes (MDS) with 10-30% blasts in the BM and hematopoietic failure were treated with low-dose AraC (2 x 10mg/m^2 sc days 1-14) and rhGM-CSF (2 x 150µg protein/day sc) given either following AraC (days 15-21) or simultaneously (days 8-14) for 1-5 cycles. The majority were treated on an out-patients basis. 108 patients with refractory anaemia with an excess of blasts (RAEB, n=54), RAEB with transformation (RAEBt, n=50) or with chronic myelomonocytic leukemia (CMML, n=4) were evaluable with a median age of 65 years, range 17-80 years. A complete remission was achieved in 15 cases (14%), 11 had a partial response (10%), and 16 a minor response (15%). Stable disease was found in 35 cases (32%). There were 16 cases of toxic death (15%), progression was noted in 15 patients (14%). No differences existed between the two treatment arms with respect to response and duration of response. Major adverse events during treatment were hemorrhage (55%), infections (54%), and fever due to GM-CSF (40%). The response rate was 39% with a median duration of 12.5 months. This appears to be promising for these particular patients with bad prognosis.

Growth Factors

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MODULATION OF RADIATION-INDUCED GROWTH FACTOR PRODUCTION BY BETA INTERFERON

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Classical theories of radiation induced pulmonary fibrosis effects have focussed mainly on the late manifestations of this injury. In particular much has been made of the apparent lag period during which few changes are thought to occur. In contrast, recent experiments from our group have suggested that the adecedents of these effects occur within hours or days after exposure. The most significant changes seen in a variety of experimental systems is the early expression of specific growth factors and cytokines by pulmonary cells. Recently, studies from our laboratory, as well as clinical experience, has suggested that pulmonary fibrosis could be reduced by pretreatment by beta-interferon. In the present studies we sought to determine if the mechanism of action of this agent is through the alteration of the production these growth factors. The human monocyte/macrophage cell line, U937 was placed in culture and maintained until confluent. Cells were then treated for 2, 6, and 24 hours with 1000U/ml of human beta-interferon (betaseron, Berlex Labs.) follwed by irradiation with graded doses of radiation. Cells were then incubated for an addition 24 hours after which cells and media were harvested and analyzed, by immuoblot, for the presence of the growth factors IL-1, transforming growth factor beta(TGFb), and platelet derived growth factor (PDGF). Interferon alone resulted in an nearly 50% increase in TGFb and PDGF. When coupled with radiation this increased almost 4 fold. In addition, IL-1 was now found to be increased by 100%. These results suggest that the observed changes in pulmonary response to radiation following interferon is mediated by alteration in growth factor gene expresison and subsequent changes in target cell growth.

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THE INFLUENCE OF EPIDERMAL GROWTH FACTOR (EGF) AND TRANSFORMING GROWTH FACTOR-B (TGFβ) ON GROWTH AND INVASION OF HUMAN SMALL CELL LUNG CANCER (SCLC) CELL LINES.

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Receptors for the growth factors EGF and TGFβ, have been evaluated in a panel of 21 human SLCL cell lines. EGF receptors were detected in 11 and TGFβ receptors in 7 cell lines, in different combinations of the three known human receptor subtypes (I, II and III). Upon treatment with EGF in a few cell lines, a growth stimulation was observed, wereas TGFβ exerted a growth suppressive effect in the cell lines expressing TGFβ receptors I and/or II. The *in vitro* invasive potential was tested using the Boyden invasion assay. A correlation between *in vitro* invasion and the expression of EGF receptors was detected, as all the EGF receptor positive cell lines were invasive. No correlation was observed between TGFβ receptor expression and Boyden chamber invasion. Our results indicate that EGF and TGFβ exerts a growth regulatory effect on receptor positive SCLC cell lines, and suggest that EGF might be involved in mediating the invasive phenotype of small cell lung cancer. Updated results will be presented.