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FROM DIAGNOSIS TO THERAPY: NEW APPROACHES IN DETECTION AND CHARACTERISATION OF CIRCULATING TUMOR CELLS

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Metastatic carcinoma remains a major problem with small survival rates. Until now, routine diagnosis and therapy of different carcinomas is dependent on the analysis of distinct blood serum parameters and/or dissected solid tumour tissue. We have chosen an additional way in characterising carcinomas: a multi-parameter blood analysis searching for circulating tumour cells. As the the major way of migration is via blood stream, the detection and characterisation of carcinoma cells within the blood is likely to provide an important predictive tool for diagnosis and creation of therapy. Therefore, we combine the highly specific method of immunomagnetic purification of viable micrometastatic cancer cells from blood with the very sensitive method of RT-PCR designed for different tumor-specific and tumor-associated antigens e.g. Hormone Receptors, Cytokeratines, Growth Factors/Receptors or CEA. Detection and quantification of the different tumor markers in the cell fractions of peripheral blood mononuclear cells and purified carcinoma cells allow differential phenotyping of the circulating tumor cells.
Furthermore we study the immunological mechanisms of defence acting against tumor cells. One strategy of the organism in the struggle for survival against tumor growth is the generation of natural killer cells. In preliminary experiments we analysed the function of NK cells isolated from tumor bearing patients in adhesion and killing of tumor cells and the role of CD95/CD95L in this process.

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Antimetastatic Effect of a Standardized Mistletoe Preparation on B16 Melanoma Cells in Mice

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The objective of the present study was to investigate the influence of a standardized mistletoe preparation (SMP) on the formation of lung metastases in mice.
Twenty five male Balb/c mice were devided into 5 groups and received a single i.v. injection of $5x10^4$ B16 murine melanoma cells. After 1 hour three groups were treated daily and intravenously for three consecutive weeks with SMP (Lektinol®, Madaus AG, Köln, Germany). Corresponding to bioactive mistletoe lectin, the dose levels were 3, 30 or 150 ng/kg body weight. Another two groups received the placebo only (negative control) or were treated with 10 µg rhIL-6/kg i.v. (positive control) at the same time points. At termination, the mice were sacrificed and broncho-alveolar lavage was performed on each animal.
As a result, there were statistically significantly increased numbers of macrophages and less melanoma cells in the lungs of all groups receiving either SMP or rhIL-6 when compared with the negative control. In addition, $CD4^+$ $CD8^+$ thymocytes were increased in the groups treated with SMP.
From the present findings, we conclude that under the conditions of this experiment a standardized mistletoe preparation (SMP) might have antimetastatic effects by stimulating the immune system in mice.

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ANGIO-GENESIS-INHIBITION AND INTRA-ARTERIAL CHEMOTHERAPY - A NEW MODALITY TREATMENT FOR ADVANCED AND METASTATIC PANCREATIC CARCINOMA.

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Introduction: Pancreatic cancer is resistant to most chemotherapeutic regimes and the results for improvement of quality of life and survival are dismal. The pattern of metastatic spread is largely defind to the upper abdominal organs within the arterial supply of celiac axis leading us to the use of intra-arterial chemotherapy in order to reach high regional drug concentrations. Due to the fact that pancreatic tumor cells over express growth factors contributing to tumor aggressiveness we tried to inhibit angio-genesis using low-dose *suramin* and *tamoxifen as a combined treatment*.
Patients and methods: 28 consecutive patients with advanced pancreatic cancer (UICC stage III 7, stage IV 21) were treated by a minimum of two cycles of chemotherapy via an angiographie catheter in the celiac axis. 20 out of 28 patients were pretreated by surgery, chemotherapy and/or radio-therapy. Karnofsky performance status was 100 in 2 pts., 90 in 3 pts., 80 in 13 pts., 70 in 7 pts. and 60 in 3 pts. Out of 28 patients (male 10, female 18) 21 had liver metastasis. The schedule consisted of two different parts: 1. Angio-genesis inhibition by low-dose *suramin* 200 mg i. v. per week, *tamoxifen* 30 mg twice a day. 2. I. a. chemotherapy 210 mg *paclitaxel* over three hours on day one, 50 mg *cisplatinum* over 60 minutes on day two, 1500 mg *5-Fluorouracil* over 24 hours on day one and two, 7500 mg *treo-sulfan* over 60 minutes on day three. Treatment free intervall was 28 days.
Results: According to WHO criteria there were 1 CR, 3 PR leading to re-operation and resection and 6 PR (remission rate of 36 %). In 14/26 patients there was a stabilisation in disease (8/28 MR, 6/28 SD) with an improvement in quality of life and reduction of pain symptoms. Grade 3 / 4 hämatologic toxicity was observed in 6 out of 28 patients, Grade 2/3 gastrointestinal in 10 of 28 patients, alopecia in 10 of 28 patients, 1 patient up to now died due to complete caval thrombosis and another patient by acute hepatic failure.6 months survival rate is 82 %.
Conclusion: This pilot study shows that the combination of chemotherapy and inhibition of angio genesis is effective in the treatment of pancreatic cancer combined with a low rate of side effects