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PROGNOSTIC FACTORS OF ADVANCED COLORECTAL CANCER PATIENTS RECEIVING CYTOTOXIC CHEMOTHERAPY

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139 patients with histologically proven residual,recurrent or metastatic colorectal carcinoma receiving chemotherapy in various phase II and III trials were retrospectively analyzed for factors influencing tumor response and survival. The analysis was based on 35 characteristics surveyed or measured at the start of chemotherapy for the advanced disease including 15 parameters from laboratory assays measured pretherapeutically. All 35 factors were examined for prognostic relevance by the multivariate regression model introduced by Cox for censored survival data.

Strong prognostic value ($p < 0,01$) showed the performance status, loss of weight, alkaline phosphatase, albumin, white blood cell count (WBC), hemoglobin, blood sedementation rate (BSR) and sex. Some prognostic value ($0,01 \leq p < 0,1$) had the site of primary tumor, extent of operation, lymphnode involvement, body mass index, CEA, LDH, protein, creatinine, size of primary tumor, and location of metastases. In a multivariate step down procedure the most important prognostic factors were identified. The four variables sex, performance status, WBC and BSR were sufficient to explain survival differences and were used to construct a final regression model. Based on these variables we calculated an individual risk score for each patient and subdivided the examined population by use of the survival curves, the observed median survival times and the relative risk estimates into different risk groups. On the base of this prognostic index four risk groups with a median survival of 1,6; 5,2; 8,0 and 16,2 months were generated.

A treatment comparison in clinical trials requires the definition of relatively homogenous risk groups of patients, as defined in our analysis, and adjustment for prognostic factors.

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FIBRONECTIN (FN) CONCENTRATION IN PLASMA OF CANCER PATIENTS

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Since there are only a few studies on the plasma-FN levels in a limited number of patients with cancer, showing conflicting results,we measured the plasma-FN by laser-nephelometry in 140 cancer patients,taking the typ of tumor and the tumor staging into account. Patients with complicating conditions such as DIC, severe liver insufficiency or infections were excluded.

	1	2 non metastatic	3 metastatic	sign. 2 vs.3
cancer total	44,3 ± 10,3 n = 140	37,1 ± 9,1 n = 81	53,2 ± 12,4 n = 59	p<0,05
breast	42,8 ± 15,0 n = 34	39,2 ± 7,7 n = 19	49,9 ± 14,3 n = 15	p<0,05
stomach + colorectal	46,9 ± 14,2 n = 45	39,6 ± 7,5 n = 25	49,2 ± 10,0 n = 20	p<0,05
lung	61,2 ± 18,3 n = 34	44,5 ± 10,3 n = 11	67,3 ± 15,1 n = 23	p<0,01
testis	33,2 ± 6,5 n = 16	29,8 ± 4,7 n = 12	39,2 ± 3,1 n = 4	n.d.

Patients with metastatic carcinoma had significantly higher plasma FN levels than cancer patients without metastasis. The plasma FN levels of cancer patients without metastasis were not significantly raised compared to normal plasma FN levels (25-40 mg/dl), while those of patients with metastatic carcinoma were distinctly above normal values with the exception of cancer of the testis.

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IMMUNE RESPONSE TO CARCINOMA OF THE LARGE BOWEL

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To test the hypothesis that carcinomas of the large bowel can provoke an immune response in vivo, peripheral T-cells from patients with metastasing tumors were analysed for their expression of activation-associated antigens and their ability to recognize the colon carcinoma cell line SW 1116. Controls including healthy persons, patients with pancreatic carcinomas and adhesion to a bronchial carcinoma cell line. Preparation of T-cells was performed by panning procedures, their phenotypic characterization by fluorescence activated flow cytometry. Recognition of tumor cells was assessed in a cell adhesion assay. It was found, that a subfraction of patients with colon carcinomas exhibit an increased number of T-cells displaying activation-associated antigens on their cell surface compared to normal controls. Moreover, these patients have elevated numbers of peripheral T-cells which show the ability to adhere to the colon carcinoma cell line SW 1116. Adhesion to a bronchial carcinoma cell line was less pronounced. Normal controls and patients with pancreatic carcinomas have significantly lower numbers of adhering peripheral T-cell. In case of pancreatic carcinomas this is however, not significant. A subfraction of adhering cells display activation associated antigens. This subset is characterized by the display of the T4 antigen, whereas only a minority expresses T8 and Leu7 (=natural killing). These experiments suggest, that an immune response to carcinoma cells is detectable in the peripheral blood of patients with advanced carcinomas of the large bowel. Moreover, these data constitute basic conditions for isolating and in vitro expanding cytotoxic autologous cell clones for therapeutic purposes.

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Liv 01

CYTOGENETIC ANALYSES OF NORMAL AND DIETHYLNITROSAMINE-INITIATED PRENEOPLASTIC HEPATOCYTES

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Rearrangements, translocations, amplifications and deletions of genomic sequences are thought to be of major importance for the expression of the neoplastic phenotype during carcinogenesis. Karyologic abnormalities have also been observed in rat hepatomas induced by chemical carcinogens. However, it is not known whether karyotypealterations in manifest hepatomas are an essential prerequisite for the development of this tumor or merely a consequence of chromosomal instability during tumor progression. An attempt was therefore made to analyse changes of the karyotype in preneoplastic rat liver cells at early stages of development and to compare those with the karyotype of normal proliferating hepatocytes after partial hepatectomy.

To obtain mitotic cells from normal regenerating adult rat liver, male Wistar AF/Han rats were partially hepatectomized. After i.p. injection of colchicin (8.5 µg/kg given at 24 and 26 hr after partial hepatectomy (PH)) the liver was perfused at 28 hr after PH through the portal vein with collagenase solution (0.05%) to isolate hepatocytes (P.O. Seglen, Methods Cell Biol.13:29-83,1976). Mitotic cells were analysed after staining with the trypsin-Giemsa technique (C. Özkinay, F. Mitelman, Hereditas 90:1-4,1979). Preneoplastic liver cells were isolated from liver of rats which had been treated for 60 days with diethylnitrosamine (5 mg/kg/die in drinking water), (H.M. Rabes, P. Scholze, B. Jantsch, Cancer Res. 32:2577-2586,1972). After collagenase perfusion of the liver the cells were cultivated in Falcon plastic flasks as described (R. Kerler, H.M. Rabes, Verh. Dtsch. Krebsges.,1986). Chromosomal analysis was performed with normal hepatocytes and different preneoplastic cell lines at various stages of development. All of the preneoplastic lines showed alterations of the karyotype when compared with the normal pattern, inclucing variations in the number of chromosomes and various marker chromosomes with translocations and deletions. There are indications that aberrations increase in frequency and severity with time in culture shedding some doubt on their biological significance during carcinogenesis in vivo. However,since not all of these lines are tumorigenic after transplantation into nude mice, it is expected that chromosomal aberrations involved in the expression of tumorgenicity in a preneoplastic cell line can be defined with this system.

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