

6.

GALACTOSYLTRANSFERASE IN MALIGNANT EFFUSIONS

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Galactosyltransferase activity (GT, E.C.2.4.1.22) and immunoactivity were determined in 69 malignant, cytology positive effusions. Enzyme activity was measured using free N-acetylglucosamine as acceptor substrate; immunoactivity was determined by ELISA using a polyclonal rabbit antiserum against the soluble human milk enzyme.

The tumor types analyzed included ovarian (9), breast (15), lung (12), gastrointestinal (12) and miscellaneous cancers (21). The median value of specific GT-activity was highest for ovarian cancer (0.57 U/L) as well as the mean value (0.80 U/L) with a range from 0.11 to 2.25 U/L. For comparison mean serum reference value for GT is 0.29 U/L. These values suggest that effusion GT is generated by cancer cells and that the determination of its level in effusion may be helpful in the diagnosis of ovarian cancer.

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7.

THE MEMBRANE-ASSOCIATED γ -GLUTAMYL TRANSPEPTIDASE (γ -GT) IN THE DIAGNOSIS OF ACUTE LEUKEMIAS (AL).

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Ficoll-enriched blast suspensions from 92 patients with AL were classified using surface markers, morphology and cytochemistry. The cells were biochemically assayed for the plasma membrane associated γ -GT and terminal transferase (TdT). In myeloid leukemias (n=37) we observed an increase of γ -GT activity in immature AML (FAB-M1, median: m = 18.3 u; u = nmole/hr/10⁶ cells). This activity gradually decreased in more mature AML (FAB-M2-M3, m = 10.2u). The level of γ -GT in granulocytes was 11.5u. Myelomonocytic and monocytic AL showed the highest γ -GT values (m = 29.7u in M4 and 30.2u in M5). Extremely high values (150-250u) were only recorded in M4 and M5 AL. The value for monocytes was 2.5u. In lymphoblastic leukemias (n=41), however, the γ -GT was very low (m=1.5u for c-ALL and 2.1u for T-ALL). The median was 9.0u and 14.0u in normal T and B lymphocytes. Interestingly, γ -GT values had a bimodal distribution in patients with acute undifferentiated leukemias (AUL, n=14): 9 patients had values between 0 and 2.8u and 5 between 7.0 and 21.0u. The correlation with TdT allowed to define 3 types of AUL: a) lymphoid-like (TdT+, low γ -GT); b) myelomonocytic-like (TdT-, high γ -GT); c) undifferentiated type (TdT-, low γ -GT). 13 of 14 AUL cases fitted in these 3 categories. As γ -GT activity is nearly absent in lymphoid AL and elevated in myeloid and monocytic AL, this enzyme may be a helpful marker for the distinction between myeloid and lymphoid leukemias.

8.

ENZYME CHARACTERISTICS OF PLASMA MEMBRANE IN CELLS FROM NON-HODGKIN LYMPHOMAS (NHL). G.A.Losa. Laboratory of Cellular Pathology, Istituto cantonale di Patologia, 6604 Locarno, CH.

The activity profiles of marker enzymes associated with the plasma membrane were investigated on cells isolated from lymph nodes of patients with malignant NHL. The composition of the population was assessed by testing cells for the presence of surface immunoglobulins (Sig) and T antigens, and of non specific esterase. Activity levels of plasma membrane enzymes involved in purine metabolism, as 5'-nucleotidase (5'-AMPase) and nucleotide phosphodiesterase, in ion transport as adenosine triphosphatase and alkaline phosphomonoesterase, and in amino acid transport as γ -glutamyltranspeptidase (GLUPAase) were assayed at saturating concentration of substrate. Cases of NHL with a majority of cells bearing Sig denoted a significant lower activity level of 5'-AMPase in comparison of cells of non malignant lymph nodes. In contrast, NHL with abundant cytoplasmic immunoglobulins (CIG) displayed a significant higher activity of this enzyme. A third group included NHL cases with a variable proportion of lymphoid cells bearing either B or T markers but without detectable CIG. Correlations be-

tween the various enzyme activities were absent with the exception for 5'-AMPase and GLUPAase. These findings indicate that the cellular heterogeneity of NHL is reflected by the enzymatic heterogeneity of the plasma membrane which in turn may relate to biological peculiarities of malignant cells.

9.

TUMOR DETECTION WITH RADIOLABELLED ANTIBODY: HOW PRACTICAL IS THIS METHOD? G.K. v. Schulthess¹, Ch. Lee¹, U. Hug², R. Andres³, F. Buchegger⁴, J.P. Mach⁵, W. Weihe⁶, R. Amgwerd² and A. Bekler¹, Institute of Nuclear Medicine¹ and Departement of Surgery², Kantonsspital CH-9007 St. Gallen, EIR Swiss Reactor Institute³ CH 5303 Würenlingen, Biochemistry Institute⁴ and Ludwig Institute⁵, CH-1066 Epalinges and Central Animal Laboratory⁶ Univ. Hospital CH-8091 Zürich, Switzerland.

With the development of monoclonal antibodies and new Nuclear Medicine techniques, there is great hope that improved tumor detection and localization by immunoscintigraphy will be possible. Tumors which concentrate the radiolabelled antibody may be better detected by scintigraphy than by morphological abnormalities. We report here on the initial clinical experience with this method at our hospital as well as on experimental results obtained in nude mice bearing human colon carcinoma using in both cases a well characterized monoclonal anti-CEA antibody No 202 labelled with ¹²⁵I. In our colon carcinoma patients, we found antibody localization in most surgical tumor specimens, but not all carcinomas could be visualized by scintigraphy. With ¹²⁵I-labelled antibody the count rates are so low that examination by emission computed tomography will present some problems. Furthermore, the topographic localization of the radioactive uptake in tumors often requires the use of an additional scintigraphy with a bone or liver seeking Technetium labelled agent. Clearly, this tumor detection method is still at a stage of clinical research. The logistics needed are formidable, it requires expert producers of antibodies, experienced radiochemists, constant quality controls, experimental models of human tumor grafted in nude mice, and an optimum collaboration between surgeons and nuclear physicians.

10.

LOCALIZATION OF COLON CARCINOMA BY EMISSION COMPUTERIZED TOMOGRAPHY (ECT) USING ¹²⁵I-LABELED F(ab')₂ FRAGMENTS FROM MONOCLONAL ANTI-CEA ANTIBODIES. J.-Ph. Grob, B. Delaloye, A. Bischof-Delaloye, F. Buchegger, S. Halpern, J. Pettavel, A. Besson, F. Mosimann, L. Barrelet, V. von Fliedner and J.-P. Mach. Ludwig Institute for Cancer Research, CH-1006 Epalinges, Div. of Nuclear Medicine and Dept. of Surgery CHUV, Institute of Biochemistry and Policlinique Médicale Universitaire, CH-1011 Lausanne.

Eleven patients with known colorectal carcinomas were injected each with 1.5 mg of F(ab')₂ of monoclonal anti-CEA antibodies No 35 and 202 labeled with 3-4 mCi of P-5n ¹²⁵I. ECT was performed in all patients 6, 24 and 48 h after injection using a double head Rotacamera. In all 5 patients with localized carcinoma (4 primary tumors from the caecum, right colon, sigmoid and rectum, respectively, and 1 sigmoid recurrence), the tumors were clearly detected by ECT. In 2 patients, tumor to normal tissue radioactivity ratios were measured on surgically resected material at day 5 post injection and found to be 6, 8, 15 and 9 for one patient and 3, 5, 7 and 2 for the other, in comparison with normal mucosa, serosa, fat and blood, respectively. Two out of 2 bone metastases, in the sacroiliac area and in the scapula were also detected, one of which was previously unknown. In 1 patient under chemotherapy 2 small lung metastases were not detected. Out of 6 patients with liver metastases, 2 remained negative, while in the 4 others, the metastases presented as cold area at the 6 h ECT. These defects progressively filled with radioactivity at later ECT in 2 cases and gave doubtful uptakes in the 2 others. Briefly, 9 of the 14 tumor sites were localized by ECT, 2 were doubtful and 3 negative. The excellent definition of the tumor in the positive cases represents an improvement over previously reported results.

11.

IMMUNOSCANNING OF GI TRACT ADENOCARCINOMAS USING TUMOR SPECIFIC MONOCLONAL ANTIBODIES (MoAb): A PROSPECTIVE STUDY. JY. Douillard, PA. Le Hur^{*} and JF. Chatel, CRLC-INSERM U.211-Hopital St Jacques, CGI (Pr Visset) 44035 NANTES CEDEX F-

Twenty-three patients with a suspicion of GI tract adenocarcinoma (primary tumor, recurrence or metastasis that could not be proven by conventional methods (X ray, Ultrasonography, endoscopy, CT scan.) were injected with radiolabeled MoAb proven to react with adenocarcinoma cells from the GI tract.

Anti-CEA mouse MoAb, produced by JP Mach (Ludwig Inst., Lausanne, Switzerland) were injected IV as 500 µg of intact immunoglobulins, ¹³¹I labeled according to the iodogen technique to a specific activity of 5 to 10 µCi/µg. Mouse MoAb 19-9 and 17-1-A provided by H. Koprowski (Wistar Inst., Philadelphia, USA) labeled with ¹³¹I to a specific activity of 2 µCi/µg were injected IV as 1 mg of F(ab')₂ fragments. A mixture of 2 out of the three antibodies mentioned above was infused 22 out of 27 times, and scanning was performed up to 7 days after injection. Final diagnosis was obtained by pathology (14/27) or on clinical evolution (13/27). Overall specificity of the method was 100% (10/10) with no false positive results, sensitivity yielded to 59% (10/17) with 7 false negative results and accuracy happened to be 74% (20/27). According to our limited experience, three major indications could be selected prospectively: 1) Isolated elevation of serum tumor markers, 2) Non convincing evidence on conventional methods, 3) Staging of GI carcinoma prior to surgery. In most cases, failure of the method was observed in peritoneal carcinomatosis (4/7) or when recurrence occurred behind the bladder, making image analysis difficult due to urinary clearance of ¹³¹I. Improvement of the technique could be expected from more appropriated radiolabel than Iodine and possibly from single photon emission tomography along with the association of several MoAb sharing similar tumor cell specificity but reacting with distinct epitopes.

12.

ESTIMATION OF CIRCULATING IMMUNE COMPLEXES IN CANCER PATIENTS: SENSE OR NONSENSE? M. Bertschmann, J.P. Späth, U.E. Nydegger and E.F. Lüscher, Theodor Kocher Institute, University of Berne and Blood Transfusion Service, Swiss Red Cross, Central Laboratory, CH-3000 Bern 9, Switzerland.

Since the detection of blocking factors in serum of cancer patients and the identification of circulating tumor-antigen-antibody complexes (CIC) as the active entities a large body of data has accumulated from experimental animal models and cancer patients in the hope to use levels of CIC as parameters for diagnosis and/or prognosis of malignancies. In the present experiments CIC were sequentially determined in serum samples from DBA/2 mice bearing histocompatible P-815 mastocytomas. 125I-Clq binding assays and Raji cell binding assays were used according to standard procedures. The tumor model is characterized by a transient phase of spontaneous regression correlated with proliferation and differentiation of cytotoxic T cells. However, regression normally changes to progression and not only T- but also B cell proliferation is observed. Since no functional correlate of B cell stimulation in the form of circulating or tumor cell bound antibody could be detected so far, tests were performed for detecting antibody in the form of CIC and for correlating CIC levels with tumor development. Despite the wide variation in tumor development elevated levels of CIC were not detected, neither in the 125I-Clq binding nor in the Raji cell binding assay. Reference complexes formed between soluble tumor cell membrane proteins and allo-antibody, however, were easily detected. These negative results are in accordance with recent negative results in mammary cancer patients (Krieger et al., Int. J. Cancer 31, 207, 1983). They support a more critical evaluation of the usefulness of CIC determination for diagnosis and/or prognosis of malignancies.

13.

MONOCLONAL ANTIBODIES AGAINST HUMAN LUNG CARCINOMAS. R. Stahel and S. Bernal, Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA 02115, U.S.A.

Mouse monoclonal antibodies were generated against cell lines of human lung adenocarcinoma (SLC40) and small cell carcinoma (OHL). SLC40 grows as cellular aggregates in suspension culture and forms glandular structures in nude mice. The antibodies LAM2 and LAM3 are strongly reactive with the surface membrane of SLC40, as demonstrated by indirect immunofluorescence and radioimmunoassay. LAM3 is also reactive with several lung adenocarcinomas growing as adherent or suspension cells in culture, but not with other adenocarcinomas, including colon and pancreas. LAM3 may be helpful in distinguishing adenocarcinomas of the lung from other carcinomas. In contrast, LAM2 is reactive with several carcinomas that grow as suspension cells in culture, including small cell carcinomas, lung adenocarcinomas, mesothelioma and seminoma. Little or no reactivity was observed with 18 carcinoma cell lines that grow adherent to the culture dish. Thus, LAM2 recognizes a surface membrane antigen that is present primarily in carcinoma cells that lack anchorage dependence in vitro. Model systems are being used to evaluate the correlation between LAM2 reactivity and metastatic potential in vivo. The antibody SMI1 is strongly reactive with cell lines and tissues from small cell carcinoma of the lung but not with most other cancer cells and normal tissues. We have found SMI1 to be useful in identifying small cell carcinoma in tissue sections and in bone marrow aspirates. Since SMI1 is highly cytotoxic to small cell carcinoma in the presence of complement, it may also be useful for therapy. SMI1, LAM2 and LAM3 are unreactive with normal bronchus, normal bone

marrow cells and leukemic cells. These antibodies may be useful in studies of differentiation and biologic behavior of lung cancer cells; they could also be important in the diagnosis, staging and treatment of lung cancers.

14.

COMBINATION CHEMOTHERAPY WITH CISPLATIN, ADRIAMYCIN, ETOPOSIDE AND CYCLOPHOSPHAMIDE FOR SMALL CELL CARCINOMA OF THE LUNG (SCLC). J.P. Dumont, J. Klasterky, J.P. Sculier, D. Bequart, G. Vandermoten, P. Rocmans, P. Libert, P. Ravez, J. Michel, E. Longeval, A. Fiesale, P. Mommen, Institut Jules Bordet, Université Libre de Bruxelles, Bruxelles, Belgique

Combinations of cisplatin (C), adriamycin (A) and etoposide (Vepesid - V) (Cancer 50, 652, 1982) or A, V and cyclophosphamide (Endoxan - E) (Cancer Treat. Rep. 66, 221, 1982) are effective in the management of SCLC. We evaluate a 4-drug combination consisting of C (60mg/m²), A (45mg/m²), V (80 mg/m² di, 2, 3) and E (1g/m²) every 3 to 4 weeks in patients with proven SCLC; 40 patients were evaluated so far after 3 courses of therapy. The median age was 54 years and the initial median performance status was 75 (Karnofsky's scale):

	Limited disease	Extensive disease
Evaluable patients	24	16
Complete remission (CR)	6 (25%)	0 (0%)
Partial remission (PR)	15 (62%)	9 (56%)
CR + PR	21 (87%)	9 (56%)

Toxicity was moderate: leucopenia grade IV was observed in 11 (27%) and grade III in 10 (25%); serious (grade III and IV) extra-hematologic toxicity (nausea, vomiting, alopecia, diarrhea, stomatitis, infection and metabolic abnormalities) was rare, except for alopecia.

Treatment was continued for a total of 10 courses or until progression. Patients with LD and PR received thoracic irradiation (5000r) and those with CR prophylactic brain irradiation. Six months after therapy 5/6 patients with CR after 3 courses of CAVE are still alive without evidence of progressive disease; the corresponding figure for PR's is 14/24.

Although final conclusions can only be drawn after evaluation of more patients and longer follow up, it appears that CAVE does not result in an increase rate of response as compared to CAV or AVE.

15.

AUTOLOGOUS MARROW TRANSPLANTATION (AUTO M.T.) IN ACUTE LEUKEMIAS: MARSEILLE EXPERIENCE IN 28 PATIENTS (PTS). D. Mazoni, B. Mascaret, J.A. Gastaut, G. Sebahoun, N. Tubiana, G. Novakovich and Y. Carcassonne, Marrow Transplant Unit and Blood Bank, Institut Paoli-Calmettes (IPC) Marseille 13273 - France -

18 pts received auto MT after high dose Melphalan (HDM 140mg/m² I.V. n=17 pts) or BACT (n=1 pt): all these pts were in relapse and had measurable disease. In AML 10/12 achieved complete remission (CR), in ALL 2/3 achieved CR, in blast crisis of OML 2/2 achieved PR. The pt receiving BACT for ALL in relapse achieved CR. Thus high dose chemotherapy is able to induce new CR or PR in high proportion of pts with leukemia in relapse (15/18 evidence of response - 83%, 13/18 CR-72%). 10 pts received auto MT after HDM (8) or BACT (n=2) as a consolidation of previous remission and are not evaluable for response. In 13 pts no attempt was done to purge marrow, and no maintenance therapy was done after the graft: all relapsed except one with AML in relapse who is in second non maintained CR 17 mths+. 8 pts had new marrow aspiration, received second course of HDM and auto MT as a consolidation and in vivo treatment of their marrow: 2 pts died in CR, 2 relapsed, 4 are in continuous CR 29 mths+, 28 mths+, 15 mths+, 9 mths+ after the first auto MT, 4 pts with ALL received I.V. Methotrexate (MTX) after auto MT (Seattle protocol for allogeneic MT): one died from pneumonia, 3 are in continuous CR 4 mths+, 3 mths+, 2 mths+, 3 pts received BACT and auto MT after complement + CALLA treatment of their marrow: all engrafted, one relapsed at 4 mths and is alive 9 mths+, one died from pneumonia within one mth, one is alive in continuous CR 3 mths+. High dose chemotherapy followed by auto MT is an efficient treatment for leukemic pts. Marrow contamination of the graft has to be considered as a limiting factor; marrow contamination might be treated by immunological, pharmacological means...

16.

TOTAL BODY IRRADIATION (TBI) AND CYCLOPHOSPHAMIDE (Cy) AS A CONDITIONING REGIMEN OF ALLOGENEIC MARROW TRANSPLANTATION (ALLO M.T.): INVESTIGATION OF SINGLE DOSE VERSUS FRACTIONATED REGIMEN OF TBI. D. Maraninchi, D. Baume, J.A. Gastaut, B. Mascaret, J.P. Guillet, R. Amalric and Y. Carcassonne, Marrow Transplant Unit, Institut Paoli-Calmettes (IPC) Marseille 13273 - France -

We investigated in 33 patients (pts) with hematologic malignancies different TBI regimen as a preparation of allo M.T.. 5 pts received 1000 rads TBI (lungshielding 800). 4 pts received 200 rads per day for 5 days. 11 pts received 220 rads per day for 5 days, 7 pts received 240 per day for 5 days. Irradiation source was linear accelerator saturne. Lungshielding