Lun 06

THE EFFECTIVENESS OF DRUGS AND THE SIGNIFICANCE OF MONOCLONAL ANTIBODIES IN EIGHT HUMAN SMALL CELL LUNG CARCINOMA (SCLC) XENOGRAFTS

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The low cure rate of SCLC has not improved in recent years. Experimental models are necessary to select new antitumor drugs or combinations and to understand the tumor biology. Therefore, we developed tumor models by transplanting 14 human SCLC into nude mice. By histopathological examinations all xenografts resembled the original tumors closely and were typical of SCLC. Tumor take occurred in 8/14 biopsies. The median doubling times in serial passage ranged from 8 to 22 days, the number of serial passages from 2 to 29.
Original SCLC tumor cells and xenograft tumors were tested by the immunoperoxidase method with MoAbs defining transferrin receptor (OKT9), neuronspecific enolase antigen (NSE), the human leucocyte antigen (HLA class I), the common leucocyte antigen (HLe-1), tumor associated antigens (BAS10, SAM12), and CEA. There seems to be a pattern of MoAbs associated with SCLC. All of the SCLC cells were negative for HLe-1 antigen, and most of the cells lost the HLA class I antigens. On the other hand, there is a strong reaction with the following MoAbs: OKT9, SAM12, BAS10 and NSE. CEA was only expressed on some SCLC tumors. There is no difference between antibody patterns of original cells and passages of nude mice. The response to drugs was studied in 6 subcutaneously growing tumors in nude mice. 2/6 responded to ADR, 2/3 to CY, 3/3 to VIND, 2/6 to PLAT, 2/3 to VP16, 1/2 to MITO, 2/2 to HECNU.
In conclusion 8 models for SCLC were developed and their chemotherapeutic response was determined. Using a series of MoAbs, there seems to be a characteristic pattern for SCLC.

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Lun 07

PATIENT SELECTION IN A RANDOMIZED LUNG CANCER TRIAL

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Randomized clinical trials are sometimes criticized as being scientific experiments that yield results which cannot be generalized to the clinical practice. This is said to be due to the numerous criteria for patient eligibility, which may produce a selected study population. In most publications of clinical trials the selection effects resulting from exclusion criteria remain unclear, because no data on the representativity of the study population are reported. - Between July 1981 and November 1983 the Rohrbach Clinic, Heidelberg, participated in a German multicenter study on the combined chemo- and radiotherapy of small cell lung cancer (SCLC). All patients, who showed up at this institution with first diagnosis of SCLC in the same time period but were not randomized into the study, were documented retrospectively with information on prognostic variables, reasons for ineligibility, course of treatment and survival time. The statistical analysis of these data gave the following results: (1) Of 282 patients with SCLC only 85 (= 30%) were entered into the trial. (2) Overall, randomized and non-randomized patients were similar with respect to the major prognostic factors, but the group of excluded patients was much more heterogenous. (3) Median survival was 10 months for the study group compared to 7 months for the group of excluded patients. (4) In retrospect, the exclusion of patients older than 70 years appeared to be unnecessary. - This analysis gives some evidence showing that participation in a clinical trial with randomized allocation to a fixed treatment protocol is at least not of negative prognostic value for the individual patient. General implications are that in future clinical trials each single exclusion criterion should be critically questioned for its clinical and methodological relevance, and baseline data on all excluded patients should be collected prospectively.

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Lun 08

SEQUENTIAL COMBINATION CHEMOTHERAPY WITH OR WITHOUT RADIOTHERAPY IN SMALL CELL LUNG CANCER (SCLC).

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The purpose of the current study was to evaluate the efficacy of sequential combination chemotherapy ± radiotherapy on remission rates and survival in SCLC. Seventy-four patients (pts) - 73 men; age 32-71 years; Karnofsky status 50-100% - were randomly assigned to receive initial chemotherapy every 3 weeks with either ACO (Adriamycin 60 mg/m² iv day 1, since 1984 Epirubicin (EPI) 40 mg/m² iv days 1+2; Cyclophosphamide 750 mg/m² iv days 1+2; Vincristine 1.5 mg iv days 1,8,15) or ETP/DDP (Etoposide 200 mg/m² 24 h-infusion days 1+3; Cisplatin 80 mg/m² 6 h-infusion day 5). Cross-over to the alternative regimen was performed at maximum tumor response, usually after 3 courses. Limited disease (LD) pts in complete remission (CR) randomly received either involved-field thoracic irradiation (40 Gy) or no further therapy.
To date, 69 pts (45 LD, 24 ED) are evaluable for response. Employing extensive restaging procedures including re-mediastinoscopy, 22 (49%) CR and 13 (29%) PR could be induced in LD pts, comparing to 5 (21%) CR and 12 (50%) PR in ED pts. A(EPI)CO and ETP/DDP each as the second regimen increased the CR-rates obtained with the alternative combination. Median survival times were 13 months (CR 18) in LD and 9 months (CR 15) in ED pts ($p < 0.01$). In LD pts with CR following cytostatic chemotherapy, consolidating irradiation seems to have a significant impact ($p < 0.01$) on remission duration and survival (26 vs 14 months). Side effects included myelosuppression, septicemia (5%), nausea and vomiting, alopecia, and polyneuropathy.
In conclusion, sequential combination chemotherapy with A(EPI)CO and ETP/DDP is unlikely to significantly improve median survival as compared to intensive standard chemotherapy. However, consolidating radiotherapy to the primary sites may improve locoregional control in LD pts.

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Lun 09

SEQUENTIAL THERAPY OF NON SMALL CELL BRONCHIOGENIC CARCINOMA (NSCLC) WITH ETOPOSID (VP-16) AND CISPLATINUM

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NSCLC are generally considered to be poorly responsive to chemotherapy. However in about 90 % of patients at one time or another the question of chemotherapy arises when surgical an radiological therapeutic measures have been exhausted or cannot be utilized because of the extent of the disease. As a rule chemotherapy in NSCLC is palliative and this should always be considered in view of its potential to considerably reduce general well being. Response rates of 40 % have been reported with combination therapy consisting of VP-16 and Cisplatinum. Response rates of about 20 % have been reported in the literature when utilising either Etoposid or Cisplatinum as single agent therapy.
We have treated NSCLC sequentially: initially Etoposid (300 mg/m² on day 1, 3, 5; repeat day 21-28) until resistance of tumor, followed by Cisplatinum (80 mg/m² day 1 and 8, repeat day 21-28). Advantages of the sequential therapy are.
1. Ability to utilize a higher dosage for single drug therapy
2. better tolerance of the chemotherapy.
To date 42 patients have been treated with this approach. Presently 23 patients have been evaluated with a response rate of 52 % (1x CR, 9x PR, 2x MR, 5x NC, 6x PD). At the time of presentation current results will be reported.

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