1099

POTENTIAL ONCOSUPPRESSOR GENES IN BREAST

Imam SA, Stampfer MS, Pathak S, and Taylor CR

University of Southern California School of Medicine, Los Angeles, CA

The present study was undertaken with a rationale that loss of certain "normal tissue antigens" might have prognostic significance, reflecting inactivation of the corresponding genes during the neoplastic progression. Consequently, an attempt was made to identify such antigens by means of generating monoclonal antibodies (MAbs) using a tolerization/immunization procedure. A MAb generated by this procedure, recognized a cell-surface glycoprotein termed luminal epithelial antigen (LEA.135). The expression of LEA.135 was determined by an immunostaining technique on mammary epithelial cell (MEC) lines in an *in vitro* model-system that consists of various steps of carcinogenesis. LEA.135 was detected on the surface of non-tumorigenic immortalized MEC. No rearrangement of chromosome 1 was observed in those cells. In contrast, LEA.135 was undetectable on oncogenically transformed or established lines of mammary carcinoma cells which were highly tumorigenic and exhibited a partial deletion of their chromosome 1. However, unlike in cell lines, LEA.135 was expressed on certain cases of primary breast carcinomas. In a retrospective study, with a follow-up ranging from 5 to 15 years, patients whose breast tumor cells exhibited the expression of LEA.135, independent of other known prognostic factors, had a superior overall survival O.S., (78% ± 0.139% at >5 yrs, p = 0.025). Furthermore, patients with poorly differentiated, aneuploid and LEA.135-positive tumor cells showed an improved O.S. (80% ± 0.179%, p = 0.013) and (90% ± 0.001%, p = 0.039) respectively than those with LEA.135-negative. The results suggest that expression of LEA.135 provides an independent estimate of clinical outcome of patients with breast carcinomas.

1100

GENOMIC INTEGRATION OF EBV IN BURKITT'S LYMPHOMA CELLS ALTERS LATENT VIRAL GENE EXPRESSION

J Wolf, M Pawlita, J Bullerdiek, A Jox, N Müller-Lantzsch, H zur Hausen & V Diehl

Medizinische Klinik I, Universität Köln, D-5000 Köln 41, FRG.

Epstein Barr virus (EBV) is supposed to contribute to the pathogenesis of Burkitt's lymphoma (BL), B-lymphoproliferative disorders in immunodeficient patients and Hodgkin's disease. Latently infected cells usually harbour multiple episomal copies of the virus. Recently, integration of the virus into the host cell genome has also been detected.

To approach the question whether the physical state of EBV might influence viral gene regulation, we have analyzed latent viral gene expression in somatic cell hybrids between BL cells and autologous EBV-immortalized lymphocytes. These hybrids harbour integrated (BL-derived) as well as episomal (LCL-derived) viral genomes. While the latent genes EBNA 1, EBNA 2 and LMP derived from the episomal EBV are expressed in the hybrid cells, the latent genes of the integrated virus are downregulated. Nonexpression of the integrated EBV is associated with a large deletion in the viral genome. These data provide an example that integration of EBV into the host cell genome might alter expression of transformation-associated viral genes.

Paediatric Oncology

1101

NON-TESTICULAR GERM CELL TUMORS IN CHILDREN: TREATMENT RESULTS OF MAKEI 89P/89

Göbel U, Teske C, Calaminus G for the MAKEI Study Group, Heinrich-Heine-University Düsseldorf, Germany

The treatment regimen of the cooperative study for non-testicular germ cell tumors MAKEI was stratified according to histology, localisation and stage. In non-germinoma 3-4 courses Bleomycin 15 mg/m²/days 1-3, VP 16 100mg/m²/days 1-3 and Cisplatinum 20 mg/m²/ days 4-8 were administered, followed by 3-4 courses Vinblastine 3 mg/m²/days 1+2, Ifosfamide 1500 mg/m²/ days 1-5, Cisplatinum 20 mg/m²/days 4-8 in patients (pts) with extended disease. Until January 31, 1993 47 protocol pts with malignant non-germinoma were registered in MAKEI 89: 2/47 pts relapsed and died. Primary sites were: ovary in 21/47 pts, sacrococcyx in 15/47 pts and other locations in 11/47 pts. The overall survival rate was 93%±4% (mean observation time: 54 months). Chemotherapy associated toxicity was mainly hematologic. Pneumopathy (WHO grade 4) was documented in 1 protocol pt. Grade 3 (WHO) decrease of creatinin clearance was observed in 25% of the documented pts with normalisation after therapy. Further trial targets are: wait and see in stage I tumors, protochemotherapy in immature teratomas, intensification of chemotherapy in stage III and IV.

Supported by Deutsche Krebshilfe

1102

IMPROVED PROGNOSIS OF INTRACRANIAL GERM CELL-TUMORS (GCTs): RESULTS OF THE MAKEI 89 STUDY

Calaminus G, Teske C, Göbel U for the MAKEI Study Group, Heinrich-Heine-University Düsseldorf, Germany

The treatment protocol of the German Society of Pediatric Oncology and Hematology for non-testicular GCTs employed in 1989 revised therapy recommendations for intracranial GCTs: radiation in germinoma was reduced for 6 Gy to 30 Gy craniospinal. In secreting GCTs (AFP/ß-HCG > 50 ng/ml) 2 courses Bleomycin 15 mg/m²/days 1-3, VP 16 100 mg/m²/days 1-3 and Cisplatinum 20 mg/m²/ days 4-8 were given prior to surgery followed by 2 courses Vinblastine 3 mg/m²/days 1+2, Ifosfamide 1500 mg/m²/ days 1-5, Cisplatinum 20 mg/m²/days 4-8 (cumulative DDP dose increased from 200 to 400 mg) and radiotherapy. Results: 46 protocol pts were registered until January 31, 1993; 2/27 pts with germinoma relapsed and were salvaged by chemotherapy; 4/19 pts with secreting GCTs relapsed. Chemotherapy associated toxicity was mainly hematologic. Decreased creatinin clearance as indicator for nephrotoxicity were observed in 3 pts, neurotoxicity and ototoxicity appeared in 1 pt each. Conclusions: Germinoma were radio- and chemosensitive. In non-germinoma the increase of DDP dose has improved the event-free survival form 34% (MAKEI 86) to 74%.

Supported by Deutsche Krebshilfe

1103

RANDOMIZED EQUIVALENCE TRIALS : THE EXAMPLE OF THE 6th WILM'S TUMOR STUDY OF THE INTERNATIONAL SOCIETY OF PEDIATRIC ONCOLOGY (SIOP)

C Com-Nougué, MF Tournade, C Rodary, J de Kraker, T Voûte, J Lemerle

Institut Gustave Roussy - 94800 VILLEJUIF - FRANCE

A current problem in pediatric oncology is nowadays to prove the equivalence of a new reduced treatment compared to a standard one, in order to get a better quality of life and reduce the costs of therapy. In SIOP6 study, two randomized trials, have been designed as "equivalence trials".

In Stage I : a short maintenance chemotherapy (S), using Vincristine and Actinomycin D during 17 weeks only was compared to the standard one (L) using the same drugs and lasting 38 weeks.

In Stage IIN0 : a 20 gy post operative radiotherapy (R+) was compared to no irradiation (R-). In each arm patients received additionally the same post operative chemotherapy using Vincristine and Actinomycin D.

For each of them, the main assessment criteria was the 2-year disease free survival (DFS). The two groups were compared using Dunnet and Gent procedure. The second one was the overall survival (SURV) which was analysed using a modified log rank test.

For S and L: the 2-year DFS (92% versus 88%) were proved to be statistically equivalent as well as the survival curves (5 year SURV : 95% versus 92% for S and L). For R+ and R-: the two year DFS (72% versus 78%) were also proved to be statistically equivalent. Nevertheless, equivalence could not be established for survival, in spite of a non significant difference between the survival curves (5-year SURV: 88% versus 85% for R+ and R-). Such desescalation trials need adequat analysis of the data to prove the equivalence and rise discussion in term of clinical conclusion, power of the analysis and ethical consideration.

1104

LONG-TERM ANALYSIS OF PATIENTS WITH EWING'S SARCOMA (ES) SURVIVING, PROGRESSION-FREE, LONGER THAN 3 YEARS.

Lombardi F.,Fossati-Bellani F.,Gandola L.,Gianni M.C., Gasparini M., Istituto Nazionale Tumori, Milano, Italy.

70 of 121 pts (58%) with localized ES, treated from '74 to '88, survived progression-free longer than 3 yrs from local therapy. The primary tumor was treated with radiotherapy in 44, surgery and radiotherapy in 21, only with surgery in 5. Chemotherapy was given to all patients and consisted of ADM, VCR, CTX ± DACT. Median FU was 11 yrs, ranging from 6 to 18 yrs. 16 of 70 pts (23%) failed because of local recurrence (7) or distant metastases (9). Time to relapse ranged from 40 to 168 mos (median 56 mos). 6 additional pts (9%) developed a second malignancy after an interval from local therapy ranging from 45 to 196 mos (mean 117 mos). In 3 pts an osteogenic sarcoma occurred in the previously irradiated bone, and the other 3 pts developed a breast carcinoma, in 2 within the radiation fields. In our ES series the incidence of late failure, either relapse or second malignancy, is not negligible, and a careful prolonged follow-up is recommended.