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SEQUENTIAL INTERFERON ALFA 2B with CHEMOTHERAPY in METASTATIC OVARIAN CANCER. PHASE II. STUDY.

Adorjan G.,Schuth J.,Angyal G., Szöke., Mocsary P., Kokas A.,
Municipal Hospital Nyiregyhaza Hungary,Essex Pharma Oncology Munich.

Between 1991-1993 38 untreated histologically confirmed metastatic ovarian cancer patients FIGO III-IV. where considered eligible for entry into this phase II. trial.Age 58,5 (46-67) Karnovsky Index 60-90.
Therapy included: cisplatin 80 mg/m2 IV. plus Cyclophosphamid 600 mg/m2 sequential every 28 days interval with interferon alpha 2b /Intron A/ 10Million IU IV plus 10 Million IU INF alpha 2b SC. 30 min. later. than 20 mg/m2 Doxorubicin IV.No.1 combination on 1. 3. 5. cycles ,No II. combination on 2. 4. 6. cycles in 28 days intervals Now are 29 patients evaluable for toxicity and response.Median duration of therapy were 30 weeks.Side effects:leucopenie WHO grade II-III.(29/29),trombocytopenie grade II III (10/29),nausea,vomiting ,fever (25/29),alopecia (7/29).The side effects successfully treated with paracetamol and odantsetron in this trial.
Results:CR :12 patients (41,4%) PR: 8 patients (27,6%) overall CR+PR 69%.Seven patients had NC. and 2 progressed. Time to progression:11 months.Survival not yet reached.
Conclusion:addition of interferon alfa 2b to chemotherapy increased tumor response rate and were well tolerated with no more side effects than chemotherapy alone.
Longer follow up is needed for definitive conclusion on survival.We will start phase III study with and without interferon in metastatic ovarian cancer.

Presenter:Dr.Adorjan Gusztav,Academic Hospital,Gynecology
H-4400 Nyiregyhaza,Szent istvan u.28

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EFFECT OF ALPHA-2 INTERFERON (a2-INF) FND MYELOSAN(BUSULFAN) ON HAEMATOPOIESIS AND BONE MARROU ENVIRONMENT IN PATIENTS WITH CHRONIC MYELOCYTIC LEUKEMIA(CML).

K.Abdulkadirov, O.Rukavitsin

Russian Research Institute of Hematology and Transfusiology (St.-Petersburg)

We studied trephinbiopsy specimens of 13 patients with CML. All studies were performed at diagnosis and then complete haematological remission were achived. 7 patients were treated with a2-inf (group 1) and 6 patients with myelosan(group 2). The capacity of adipose and bone tissues did not change considerably after treatment. But as a result of treatment the significally decreased capacity of megacariocytes (from 4,4+0,8% to 2,4+0,6%) and the medium number in each visual field (from 12,2+2,3 to 7,4+1,9) in all specimens of group 1 patients. The number of stromal endosteal cells decreased from 4,0+1,0 to 3,3+0,2 in this group ($p<0,05$). In contrast, the capacity of megacariocytes (from 1,7+1,0 % to 1,6+1,0%) their medium number (from 6,0+2,5 to 5,9+3.0) and the number of stromal endosteal cells did not considerably change in all specimens of group 2 patients.
We believe that the bone marrow megacariocytopoiesis might be significally supressed by a2-INF in patients with CML. One of the probable mechanisms of a2-INF action is indirect effect on myelopoiesis via stromal endosteal cells.

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CLINICAL RESULTS OF TWO DIFFERENT DOSE REGIMENS WITH HIGH-DOSE INTERFERON-ALPHA AND INTERLEUKIN-2 IN ADVANCED RENAL CELL CANCER AND MALIGNANT MELANOMA.

K. Fenchel, A. Winkler, PS.Mitrou, D.Hoelzer, L. Bergmann
Div. of Hematology, J.W.Goethe University, Frankfurt/M., Theodor Stern Kai 7, Frankfurt/M, FRG

Both, interferon-alpha (IFNα) and interleukin-2 (IL-2) have some efficacy in advanced renal cell cancer (RCC) and malignant melanoma (MM) as single agents and act additiv or synergistically on activation of cytotoxic cells in vitro. In order to improve clinical results without more toxicity, we treated patients (pts.) with RCC and MM in a daily alternating schedule of rIFN-α s.c. (Essex-Pharma, Munich) and rIL-2 (EuroCetus, Frankfurt) as 1h infusion for 14 days. In group one dose of rIFNα was $5x10^6 U/m^2$ and rIL-2 $9x10^6$ IU/m^2. In group two rIFNα dose was in an escalating manner $10\text{-}20x10^6$ U/m^2 and rIL-2 $18x10^6$ IU/m^2. Every fortnight cycle was repeated after a rest of 3-4 weeks up to a maximum of 4 cycles. Totally, 30 pts. with RCC and 21 pts. with MM entered the study, 12 RCC and 4 MM in group one, and 18 RCC and 17 MM in group two. In the first group, 12/16 (9 RCC and 3 MM) pts. are evaluable for response. The pattern of metastasis was not equally balanced within the two groups: in group one, 9 pts. showed lung or lymph node metastasis and 7 pts had metastases in bones, liver or elsewhere. Lung and lymph node metastasis is known as being correlated with a significant better response to IL-2 therapies. In group two only 15 pts showed lung or lymph node metastases, while 20 pts had metastases in liver, bone etc. One pt. with RCC achieved partial remission (PR), one with MM an ongoing CR (24+ months). In group two, 20/32 (9 RCC pts and 11 MM) pts. are evaluable: One pt. with RCC achieved PR and 3 stable disease (SD), in 2 pts. with MM PR and in one SD was observed. Therefore, remission rate for RCC in group 1 was 10%, for MM 33%. In group 2 it was for RCC 11% and for MM 20%.
In both schedules no grade IV toxicities were observed, the side effects were tolerable. No major difference between the higher and lower dosages were noted. In one case a pulmonary edema due to capillary leak syndrome in group two was observed.
The results seem not to be very encouraging, but may be explained by the inclusion of patients with metastasis patterns, which are predictive for negative outcome to immunological therapies.

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CD4 POSITIVE, HLA-DR RESTRICTED T CELL RESPONSE TO HUMAN IFN-γ TREATED SARCOMA CELLS. FUNCTIONS, SPECIFICITY AND CYTOKINE PROFILES

Heike, M., Schlaak, J., Schulze-Bergkamen, H., Herr, W., Kohlhase, V., Schmitt, U., Schneider, P*., Meyer zum Büschenfelde, K.-H., First Department of Medicine and Department for Forensic Medicine*, University of Mainz, D-55131 Mainz, Germany

CD4 positive T cells play an important role for tumor immunity in animal tumor models. Still, there are only few reports about the role of CD4 positive, HLA-class II restricted T cells in the immune response against human tumors. Here we demonstrate a CD4 positive, HLA-DR restricted T cell response in vitro against a human sarcoma, MZ-MES-1. A prerequisite for this response was the induction of HLA-DR on MZ-MES-1 cells by IFN-γ. Tumor reactive T cell clones from autologous mixed lymphocyte tumor cell cultures were exclusively CD4 positive and HLA-DR restricted. Antigens on MZ-MES-1 presented by HLA-DR 15 and by HLA-DR 4 were recognized by T cell clones. The T cell clones released TNF and additional cytokines in response to IFN-γ treated MZ-MES-1 cells. Cytokine profiles of T cell clones were either Th2 like or Th1 like and differed between cloning experiments with different experimental conditions. Both Th1- and Th2-like clones effectively lysed IFN-γ treated MZ-MES-1 cells. Supernatants of both types of Th clones induced HLA-DR-expression on MZ-MES-1 cells. The in vitro T cell response to MZ-MES-1 represents a new model for HLA-DR restricted T cell responses against human tumors. (Supported by DFG, SFB 311/C9)