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RECOMBINANT INTERFERON (IFN) ALPHA AND GAMMA ALTER THE BINDING OF PROGENITOR CELLS OF PATIENTS WITH CML TO FIBRONECTIN (FN). Elmaagacli AH*,Berthel M*,Wandl U+,Niederle N#. *Dep. of Molecularbiology, Univ.of Essen; +KKH Traunstein,#Städt.KH Leverkusen, Germany.

We have evaluated the binding of primitive progenitor cells of untreated patients (n=5) with CML to uncoated Petri dishes and coated Petri dished with purified human plasma FN.The effect on adhesion of in vitro exposure of progenitor cells to IFN-alpha or -gamma (1000 U/ml) for two hours,was examined.The levels of colony forming cells (early erythroid progenitors BFU-E and granulocytic progenitors CFU-C) of the adherent fraction was measured. Treatment with FN alone did not increase significantly the binding of BFU-E (7,4 ± 25,6 mean ±SEM), but that of CFU-C (29,15%±12,95). Treatment with IFN alone reduced the proliferation of all cells.The number of BFU-E fall about 217% for IFN-alpha and about 173,5% for IFN-gamma and for CFU-C about 208% for IFN-alpha and 99,5% for IFN-gamma. But treatment with FN and IFN resulted in again increased numbers of CFU-C with about 190,6%±108,8 for IFN-alpha and about 44,4% ±30,6 for IFN-gamma. Attachment of BFU-E increased only slightly with 2,6% for IFN-alpha and 2,3% for IFN-gamma. We conclude that IFN's can increase the expression for FN-receptors, effecting a better adhesion to the stroma.

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HIGH DOSE CHEMOTHERAPY (HDCT) VP-16, CYCLOPHOSPHAMIDE, CARBOPLATIN AND AUTOLOGOUS BONE MARROW TRANSPLANTATION (ABMT) WITH G-CSF IN PATIENTS WITH BREAST CANCER (BC). Preliminary results.

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9 pts received one cycle of HDCT with Carboplatin 1400 mg/m^2 VP-16 1200 mg/m^2 and CTX 4.5gr/m^2 divided in 3 days ABMT was followed 3 days later. 6 pts with st.IV BC in PR or CR following chemotherapy with 3 courses CAF (IMTX) and 3 pts with high risk primary BC (st.II, > 10 lymph nodes) received the same regimen as adjuvant and were eligible. The median number of mononuclear cells collected was 0,79X10^8/Kg (0,3-1,44),of CFU-GM 3,5X10^4/Kg(2,1-6,64) and of CD34+ cells 1.2X10^6/Kg (0,8-2,49). Following infusion of the CD34-selected marrow all pts received 10µg/Kg of Bd Wt G-CSF support. Median duration of absolute neutrophil count ≤ 500 cells X 10^{9}L was 11 days and platelets ≤ 20.000 14 days. 1 patient with St.IV BC died from cardiotoxicity one day after HDCT. 7/8 pts had neutropenic fever with documented infection in 4/8 pts. All pts with residual metastatic BC after induction CT responded with HDCT (2CR and 2PR).Duration of responses were 2+,3, 8+,11,12 months. Pts with St II BC are remaining NED 2, 14.15 months after ABMT.

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ERYTHROPOIETIN (rHuEPO) IN CHEMOTHERAPY-INDUCED ANEMIA

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From March 1991 to November 1992, 32 anemic cancer patients receiving various chemotherapy regimens were treated with rHuEPO in an attempt to reduce anemia.

Erythropoietin (kindly provided by Boehringer-Mannheim) was administered subcutaneously at a starting dose of 10,000 IU, 3 times weekly, with a planned dose-escalation every 3 weeks up to 10,000 IU, 5 times weekly until a target Hb value of 11 gr/dl was reached. Four patients received less than 3 weeks of treatment (3 early disease-related deaths and 1 lost to follow up) and are therefore not evaluable for antianemic rHuEPO activity. Twenty-eight patients (M/F 11/17; Median age 57 yrs; Median PS ECOG: 0) with a mean Hb starting value of 8.92 ± 0.76 are evaluable for response.The median treatment duration was 12 weeks (range 4-32) with a median weekly dose of 30,000 IU (range 10,000-50,000).

Response was defined as a ↑ 2 gr/dl Hb increase in 12 weeks: 17 of 28 evaluable pts (60.7 %) responded with a mean Hb increase of 3.73 ± 1.55 and a mean 33.42% Ht increase (% of initial value). The median time to achieve a response was 6 weeks (range 2-12), although 2 pts responded after 10 weeks. In 13 of 17 responding pts with a ↑ 11 gr/dl Hb value, the dose-escalation was not performed, 3 of whom reduced the EPO dose after reaching an Hb value ↑ 12 gr/dl.Erythropoietin was well tolerated and safely administered as home-therapy. During the study the serum transferrin, haptoglobin and ferritin levels were monitored. To date, no correlations with the antianemic response have been observed.

In conclusion these data suggest that rHuEPO, as a home-therapy regimen, can reduce chemotherapy-induced anemia in a relatively short time in most of patients.

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CHEMOTHERAPY (CT) DOSE INTENSIFICATION IN OVARIAN CANCER (OC) WITH RECOMBINANT HUMAN INTERLEUKIN-3 (RHIL-3). Gameren v MM, Willemse PHB, Mull R, Biesma B, Vries de EGE. University Hospital Groningen, The Netherlands.

Based on previous studies (Cancer Res.1991:51, 116, Blood 1992:80, 1141) we know that many patients (pts) cannot receive CT consisting carboplatin (CBDCA) 300 mg/m^2 and cyclophosphamide (Cyclo) 750 mg/m^2 for OC every 4 wks without hematopoietic growth factor support. The desirable dose of rhIL-3 based on a phase I/II study in this setting was 5 or 10 µg/kg/d. A study was designed to determine if rhIL-3 would allow CT administration every 3 wks, with 17 pts treated to date. Cyclo was administered 750 mg/m^2 and CBDCA was dose adjusted to creatinine clearance: 60-80 mL/min: 257 mg/m^2, 80-120 : 300 mg/m^2, 120-140: 340 mg/m^2, >140: 385 mg/m^2 in 6 cycles (c). RhIL-3 (5 or 10 µg/kg/d) was given sc d2-11 in each c. At 5 and 10 µg doses are 10 (46c) and 7 (33c) pts evaluable for toxicity and 10 (43c) and 7 (27c) pts for efficacy. Side effects were fever and headache controllable with acetaminophen. At 5 µg rhIL-3 in three c (2 pts) and at 10 µg in six c (5 pts) urticaria occurred. In 4 episodes dyspnea and/or oedema was observed. This reaction occurred during c3-6 and was controlled with antihistamine and prednisolone. CT could be administered every 3 wks in 43/70 c (25/43 c at 5 µg, and in 18/27 c at 10 µg (NS)), every 4 wks in 13/70 c and > 4 wks in 14/70 c. No platelet transfusions were required. Thus, in 61% of c it was possible to give a CT dose intensification of 33%. If full dose CT were to be given every 4 wks it would have been possible to administer in 80% of c in time. Conclusion: with rhIL-3 CT dose intensification of 33% is possible by reducing CT intervals, while no platelet transfusions were required.

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MONOCLONAL ANTIBODIES IN COMBINATION WITH CYTOKINES IN TREATMENT OF ADVANCED COLORECTAL CARCINOMA.

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Tumor cells express on their surface tumor associated antigens (TAA). CO17-1A is a non-secreted glycoprotein (40kD) TAA on colorectal carcinoma (CRC) cells. A mouse monoclonal antibody (mMAb17-1A) (IgG_{2a}) has been produced against this antigen. Using this MAb alone for therapy of patients (n=67) metastatic CRC 2% achieved a complete remission (CR) and further 14% of the patients minor response (MR) or stable disease (SD) i.e. total 16%. As ADCC may be an important effector function we have in in vitro systems shown that several cytokines and combinations might increase the cell killing capacity of mononuclear cells against the human CRC cell lines (SW948, SW1116) in the presence of mMAb17-1A. GM-CSF increased significantly the tumor cell lyses. 20 patients have been treated with mMAb17-1A/GM-CSF, 2(10%) achieved CR and further 1 patient a MR and 3 patients SD i.e. 30% (6/12). Combining mMAb17-1A/GM-CSF/IL-2 in vitro further significantly enhanced the killing capacity of the tumor cells. Another treatment protocol for metastatic CRC was instituted where mMAb17-1A/GM-CSF/IL-2 were combined. Twelve patients have been recruted to date. The treatment has been well tolerated. Four patients have completed the whole treatment period. One of them entered a practically complete remission. In several in vitro systems we have shown that chimer (c) MAb17-1A is significantly more effective than mMAb17-17A in ADCC. In April 1993 a new treatment series will start combining chimer MAb17-1A and GM-CSF. Results of this study as well as further results of the studies will be presented.

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OUR EXPERIENCE IN THE USE OF GRANULOCYTE COLONY- STIMULATING FACTOR (G-CSF)

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We evaluated the ability of human recombinant granulocyte colony-stimulating factor (rhG-CSF) to prevent chemotherapy-induced neutropenia or to accelerate recovery from this complication.

Patients and methods - Fifty patients were entered in this study (16 non-Hodgkin's lymphoma, 9 small cell carcinoma of the broncus, 7 advanced breast cancer, 4 Hodgkin's disease, 4 soft tissue sarcomas and others). There were 32 men and 18 women with a median age of 43,9 years (range 15-77).G-CSF was given by daily subcutaneous injection for 14 days. The total daily dose of G-CSF was 5 g/kg. 130 courses were given. The second absolute neutrophil count (ANC) was performed on day 14 of each course. Statistical analysis consisted of the Fisher's exact test and Mann-Whitney U test.

Results - 1) Prevention - 85 courses: 79 were successful (17 without increase in ANC) with an increase of x = 2.110 and 6 were not (fever, hospitalization and antibiotic therapy) with x = -5.600 (p 0.001). 2) Neutropenia - 45courses (all with elevation of ANC): 30 with febrile neutropenia (initial ANC x = 137 and increase of x = 6.870) and 15 with afebrile neutropenia (initial ANC x = 680 and increase of x = 4.600) (p 0.004 for the first ANC and N.S. for the increases). 3) Toxicity - Osteomuscular pain : 13 courses (10%) and nausea 9 courses (6,9%). Elevation of LDH in 25 courses (19%) and of alkaline phosphatase in 20 courses (15%).

Conclusions - 1) The G-CSF was an effective agent in the prevention of febrile neutropenia. The efficacy was mainly related to the ANC increase, 2) The efficacy of the G-CSF in the neutropenia was related to the initial ANC and not to the increase, 3) The toxicity was tolerable.