CML 05

TREATMENT OF CHRONIC GRANULOCYTIC LEUKAEMIA (CGL) WITH ALLOGENEIC BONE-MARROW TRANSPLANTATION (BMT)

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Survival of CGL-patients is variable but 30 months after diagnosis (median) CGL tends to reach blast crisis (BC). Allogeneic BMT is currently the only curative treatment for CGL. The prognosis of CGL after BMT is mainly determined by the stage of disease : survival after BMT in chronic phase (CP) is approx. 80%, in BC under 10% and in accelerated phase (AP) 30-40%. Between 4/82 and 10/85 14 CGL-pat. (Ph pos.) were treated with a HLA-identical BMT (12 in CP, 1 in AP and 1 in BC). CGL-pat. in CP received Cyclophosphamide and TBI, pat. with AP or BC were treated with Etoposid, ARA-C, Cyclophosphamide and TBI. GvHD-prophylaxis was performed with Mtx (n=4) or Campath I-incubation of the graft (n=10). Engraftment was demonstrated in all 14 pat. (male/female : 9/5, age : median 23 and range 18-41). 4 pat. (28%) developed an acute GvHD, one of these (7%) a chronic GvHD. 8 of the 12 CGL-pat. in CP are alive from 21 to 1211 days after BMT, 3 pat. died of BMT-associated complications and 1 pat. in late CP died of a CGL-relapse after BMT. The 2 pat. in AP or BC relapsed with BC half a year after BMT.
These results confirm the unfavourable results of BMT in CGL in AP or BC. BMT in late CP seems to be associated with a high risk for relapse as well. Hence BMT in CGL should be performed as early as possible in CP.

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VHe 01

HAEMOPOIETIC PRECURSOR CELL TOXICITY OF MITOXANTRONE*

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Mitoxantrone, a synthetic anthracenedione derivate, shows a wide range of antitumour effects via binding to DNA and thus inhibiting nucleic acid synthesis. When applied in patients with breast carcinoma, Mitoxantrone seems to be as effective but less toxic as Doxorubicin. However,the major dose-limiting toxicity is myelosuppression,especially leukopenia. For this reason and as there is increasing evidence for the antileukaemic effect of Mitoxantrone in acute leukaemia, analysis of its toxic effects on haemopoietic precursor cells seemed to be of clinical interest.

In vitro survival of human granulocyte-macrophage colony-forming cells was determined either after preincubation or after permanent incubation with Mitoxantrone of normal human bone marrow and peripheral blood cells, respectively. For both incubation shedules, the results show toxic effects of even less than 1 ng/ml of Mitoxantrone. By using HPLC, the intracellular drug concentration was below 1 ng per $2x10^7$ cells which is below the detection limit. Moreover, the results indicate the existence of two populations of precursor cells showing different sensitivity to the drug.

In order to compare these in vitro results with in vivo conditions, similar analyses of the in vivo effects of Mitoxantrone on haemopoietic precursor cells are currently under way.

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VHe 02

MYELOPROTECTIVE EFFECT OF MEDROXYPROGESTERONE ACETATE (MPA) ON COMMITTED GRANULUPOIETIC STEMCELLS UNDER CYTOTOXIC CHEMOTHERAPY

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Bone marrow toxicity is the most important dose limiting factor of any systemic cytostatic chemotherapy (CT). Originating from clinical observations it could be shown that steroid hormones exert some protective effect and that testosterone, glucocorticoids, and estrogens temper granulo-- and thrombocytopenia, shorten the suppression of the progenitor cells and increase the recovery following CT: Recently a number of clinical studies has been published suggesting decreased bone marrow toxicity, when MPA given at high doses is added to cytostatic agents. To define the action of MPA on the haematopoiesis and to exclude that the observed elevated bloodcounts merely reflect a cell shift from the marginal into the circulating pool, we designed a prospective controlled study. 18 patients with progressive disseminated breast cancer who had never been treated with CT before, were randomly assigned to one group given FAC alone (5 FU:500mg/m^2 d1+8, ADM 500 mg/m^2 d1, CPA 500mg/m^2 i.v. d1, q4w) or with additional HD-MPA (1000mg per os /day, beginning at least 1 week prior to treatment and given throughout the CTcourses).
Besides counting the peripheral blood cells we measured the "colony-forming units" (CFU'c), the presumed granulopoietic precursers of the committed stemcell compartment at weekly intervals prior to and following CT.
Under HD-MPA-treatment there is a significant reduction in growth and absolute number of CFU'c as compared to those patients, receiving FAC-CT only.
Our results suggest that MPA in a high dosis inhibits mitotic activity and differentiation of pluripotent precursors into the committed stem cell compartment, thereby saving the proliferating granulopoietic progenitor cells from the cytocidal action of cytotoxic agents.

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VHe 03

PERI- AND INTRAOPERATIVE INBALANCE IN THE HAEMOSTATIC SYSTEM OF CANCER PATIENTS

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Activation of the coagulation system may promote the formation of micrometastases. We therefore measured fibrinogen, fibrinopeptid A (FPA), AT III, FDP, $\alpha_2$antiplasmin ($\alpha_2$ap) before, during and after comparable operations performed on patients with and without cancer, 16 each.
The cancer patient group (CPG) as well as the control group without cancer showed a distinct rise in the FPA level intraoperative, indicating a considerable activation of thrombin. FPA levels in the CPG were significantly higher then in the control group throughout the course of investigation ($p<0,002$). Initially and throughout the whole course of investigation the AT III levels were significantly lower in the CPG than in the control group ($p=0,05$). Lowest values of AT III were measured in the CPG (44±14%) and the control group (56±17%) during operation. Especially in regard to the CPG, it can be presupposed that perioperative "low dose heparin" (3x5000/d) treatment of all the patients was to a large extent ineffective. A decrease of fibrinogen concentration in CPG of 50 mg/dl opposed to 14 mg/dl in the control group was found, even after intraoperative dilution was considered and corrected. An significant increase ($p<0,05$) of FDP levels was first measured postoperative. Highest levels were found on the eighth day, averaging 80±56 τg/ml in the CPG and 24±13 τg/ml in the control group. In contrast to the distinctly decreased AT III levels, α_2AP was never pathologically decreased despite intraoperative dilution in both groups. Since the development of micrometastases is dependend on fibrin formation, the inbalance between AT III and α_2AP activity respectively, might promote the formation of micrometastases during operation.

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