Northern blotting. Heparin-Sepharose fractions of CP stimulated the proliferation of freshly isolated human umbilical vein endothelial cells. This effect could be neutralized by anti-bFGF MoAb. Incubation of cell lines with bFGF-antisense oligonucleotides and pentosan sulfate resulted in a growth inhibition of some, with suramin of all samples tested. Furthermore expression of bFGF was detected by immunohistochemistry in 11/11 NSCLC sections. Our results suggest that endogenous bFGF may be involved in autocrine growth stimulation and/or neoangiogenesis in human NSCLC. Therapies aiming at interruption of this autocrine/paracrine loop may be clinically relevant.

228 ORAL

LEUKEMIA INHIBITORY FACTOR (LIF) STIMULATES THE GROWTH OF HUMAN BREAST CANCER CELLS

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Bone is the most common metastatic site of several solid tumors like breast, kidney and prostate. Both phenotypic and local factors may contribute to the growth stimulation of these cancer cells. One possible growth factor to the cancer cells might be LIF which is a multifunctional cytokine constantly expressed by bone marrow stromal cells (Estrov *et al.* 1992). To investigate this hypothesis we analyzed the effects of LIF on proliferation of metastatic breast (MCF-7, T-47D, MDA MB-231), prostate (DU-145), kidney (ACHN) and primary kidney (A-498) cancer cell lines. LIF stimulated MCF-7 colony proliferation significantly both in serum containing, and in serum- and estrogen-free, conditions. There were two times more colonies in cultures with LIF (38 to 190 ng/ml) than in control cultures of MCF-7 cells. In addition, the amount of T-47D colonies increased significantly, but less than that of MCF-7 colonies. These effects of LIF were inhibited by antibodies to LIF. LIF did not have any effect on the colony formation capacity of MDA MB-231, DU-145, ACHN and A-498 cell lines, which, on the other hand, secreted LIF into culture supernatants. No measurable amount of LIF could be detected in culture supernatants of MCF-7 or T-47D cells. According to present results MCF-7 and T-47D cells are stimulated by LIF, which makes this growth factor very interesting to further studies in cancers with bone metastases.

229 ORAL

A RANDOMIZED STUDY OF INTERVENTIONAL G-CSF THERAPY IN PATIENTS WITH FEBRILE NEUTROPENIA FOLLOWING CHEMOTHERAPY

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Febrile neutropenia (FN) following chemotherapy carries considerable patient (pt) welfare and resource use implications. It remains unclear whether cytokines commenced with antibiotic therapy hasten recovery from the septic episode.

In a double blind study, 186 paediatric pts (median age 5 yrs) commencing antibiotics for FN (neutrophils $\leqslant 0.5 \times 10^9$/l) were randomized to also receive G-CSF (Amgen) 5 μg/kg/d or placebo. Study guidelines required neutrophils at least 0.2 for hospital discharge. G-CSF/placebo was stopped at withdrawal of antibiotics or if neutrophils reached 1.0. Patients received a total G-CSF dose of 603 μg over 5.2 days. G-CSF treated pts had more rapid neutrophil recovery to $\geqslant 0.5$ (median 3d vs 5d; $P = .03$; Mann-Whitney), less use of antibiotics (median 5d vs 6d; $P = .02$) and shorter hospital stay (median 5d vs 7d; $P = .04$). Fever duration (2d vs 3d) and neutrophil recovery to 0.2 (3d vs 4d) for G-CSF and placebo-treated pts respectively were not significantly different. No G-CSF-related symptomatic or haematological toxicity was seen.

This study indicates that G-CSF therapy, initiated after the onset of FN in paediatric pts, accelerates neutrophil recovery and reduces the duration of both antibiotic usage and hospitalization.

230 ORAL

COMBINATION OF RHIL-6 AND GM-CSF IN PATIENTS BEFORE AND AFTER CHEMOTHERAPY (CT)

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In order to evaluate amelioration of CT-induced bone marrow toxicity, rhIL-6 and GM-CSF were combined in pts with breast cancer and non-small cell lung cancer. Two weeks before CT, rhIL-6 (4 pts at 2.5 μg/kg/d and 3 pts at 5.0) and GM-CSF (5 μg/kg/d) were administered for 7d sc, followed by a rest period of 7d. Then CT (mitoxantrone 40 mg/m^2 and thiotepa 10 mg/m^2, q21d) was administered. Post-CT the same combination of rhIL-6 and GM-CSF (d5-14) was given as pre-CT. The results were compared with a group (n = 7) who had received the same CT, with only rhIL-6 (also 2.5 and 5.0 μ/kg/d). Data were pooled for 2.5 and 5.0 μg/kg/d rhIL-6. Flu-like symptoms were reported frequently, and were more severe in those receiving rhIL-6/GM-CSF. In this group 1 pt experienced worsening of dyspnea. Anemia occurred before and after CT in both groups. Pre-CT a four-fold increase (P .006) in the number of leukocytes was observed for the combination, with normalization before CT. Platelets increased to 154–174% of baseline values pre-CT, without differences for rhIL-6 and rhIL-6/GM-CSF. Post-CT no differences were observed for leukocytes between both groups, platelet nadir was lower for rhIL-6/GM-CSF when compared with rhIL-6 alone, i.e. 57 vs 115 $\times 10^9$/L respectively (P .035). Pre-CT stimulation occurred for leukocytes and platelets, however, no synergism was observed for the combination post-CT.

231 ORAL

BIWEEKLY CHOP CHEMOTHERAPY WITH RHUG-CSF (LENOGRASIM) FOR AGGRESSIVE NON-HODGKIN'S LYMPHOMA (NHL) PATIENTS

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By multicenter Phase III trial, feasibility and chemotherapeutic effect of biweekly CHOP therapy, supported with rHuG-CSF (CHOP-G) were investigated for the patients with aggressive non-Hodgkin's lymphoma (NHL) except lymphoblastic lymphoma, Burkitt lymphoma and ATL. The criteria of patient's eligibility were as follows: (1) Diagnosis as NHL pathologically, (2) clinical Stage of II to IV with evaluable lesions, (3) no previous therapy, (4) age from 15 to 79, and (5) performance status of 0 to 2 with no dysfunction of major organs. CHOP-G protocol was as follows: CPA 750 mg/m^2 i.v. day 1, ADM 50 mg/m^2 i.v. day 1, VCR 1.4 mg/m^2 (max. 2 mg/body) i.v. day 1, PSL50 mg/m^2 p.o. day 1 to 5, and rHuG-CSF (Lenograsim) 2 μg/kg/day s.c. days 3–14. This CHOP-G regimen was given biweekly with 6 to 9 cycles after the patient's informed consent. Toxicity was evaluated by the worst event for each organ system. A total of 82 patients were eligible and registered on this study up to date. Average given courses of CHOP-G were 6.74, and the intervals between each course were 15.6 day. Myelosuppresson was the major side effect, and leukopenia of grade 3 and 4 by WHO criteria was experienced by less than 50% of the patients during the 9 cycles. Delay of the treatment schedule due to neutropenia, however, rarely appeared. Thrombocytopenia was acceptable, and anemia was usually noted after the 5th cycle in most patients. Complete remission rate was 76.8% in evaluable cases. Although feasibility of CHOP-G regimen was demonstrated, survival benefit is too early for the evaluation.

232 ORAL

CLINICAL AND HEALTH STATUS ASSESSMENTS IN ANAEMIC CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) PATIENTS TREATED WITH EPOETIN ALFA

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We studied the impact of Epoetin alfa therapy on hematological parameters and health status in 221 anaemic (haematocrit (Hct) < 32%) CLL patients (pts), Rai Stages III and IV, in a randomized, double-blind, placebo (pbo)-controlled trial. One hundred and forty-one pts received Epoetin alfa 150 IU/kg SC 3×/week, and 80 pts received pbo, generally by self-injection, for up to 12 weeks. Hct was measured weekly and

health status was assessed at baseline and after 6 and 12 weeks of treatment via a self-administered questionnaire combining validated psychometric scales, including energy, physical/social/cognitive role function and mental health. The two groups were comparable in baseline clinical, demographic and health status measures. Treatment with Epoetin alfa was well tolerated. The baseline Hct was 27.5 in the Epoetin alfa group, and 27.7 in the pbo group. The mean final Hct increased by 5.7 percentage points in the Epoetin alfa-treated group, and by 1.5 percentage points in the pbo group ($P < 0.0001$). Approximately 50% of the Epoetin alfa group had a Hct change of ≥ 6 points over baseline values unrelated to transfusion vs approx 15% of the pbo group ($P < 0.0001$). Overall, about 30% of the Epoetin alfa-treated pts achieved a Hct ≥ 38, unrelated to transfusion, vs approx 5% in the pbo group ($P < 0.0001$). For all pts, between group differences favouring the Epoetin alfa group were found for energy scores ($P < 0.05$). In addition, Epoetin alfa-treated pts whose Hct reached 38% showed significant improvements in energy, self-rated health, physical function, role function/physical, role function/emotional, social function, and mental health ($P < 0.01$ to $P < 0.0004$) vs pbo pts. The results show that Epoetin alfa improves Hct in anaemic CLL pts, and the impact of Epoetin alfa treatment on health status is greatest in pts showing a substantial Hct response.

233 ORAL

A PHASE IV STUDY OF EPOETIN ALFA EXAMINING CLINICAL OUTCOMES IN ANAEMIC CANCER PATIENTS RECEIVING CHEMOTHERAPY

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This Phase IV study, involving over 570 U.S. community-based oncology practices, aimed to measure clinically relevant outcomes in 2,030 Epoetin alfa-treated anemic patients (pts) with solid or hematological tumors, who were receiving chemotherapy. Patients received Epoetin alfa 150 IU/kg 3 times weekly for up to 4 months. If necessary, this dose could be increased to 300 IU/kg 3 times weekly after 8 weeks of therapy. Quality of life (QOL), mean change in hemoglobin (Hb) level and avoidance of transfusion were assessed. One thousand, four hundred and ninety-eight pts had both baseline and end values. The mean changes in energy level, activity level, and overall QOL from baseline were increased significantly (+38%, +32%, +24%, respectively; $P < 0.001$). These improvements correlated directly with a significant increase in Hb level from baseline (+1.7 g/dl; $P < 0.001$, $r = 0.254$). In the month before therapy, 22% of pts were transfused. During months 2, 3 and 4, the percentage steadily decreased (15%, 11%, 10%; $P < 0.001$ compared to baseline). Fifty-nine percent of pts were transfusion-independent after month 1. Forty-one percent of pts discontinued therapy—22% because of illness, adverse effects, or death (none drug related), 19% because of disease progression, discontinued chemotherapy, or personal reasons. In conclusion, the Epoetin alfa-treated anaemia cancer pts assessed experienced significantly improved QOL. Transfusion requirements were significantly reduced, and Hb levels increased significantly. Epoetin alfa was well tolerated.

234 ORAL

REDUCTION OF THE RISK OF TRANSFUSION IN PATIENTS WITH SMALL CELL LUNG CANCER (SCLC) UNDERGOING CHEMOTHERAPY

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This open-label, controlled, multicentre study examined the efficacy of subcutaneous (SC) Epoetin alfa (administered 3 times weekly) in preventing anaemia in 130 initially non-anaemic (Hb $\geq$ 10.5 g/dl) SCLC patients (pts) scheduled to receive 4–6 cycles of platinum-based combination chemotherapy.

Patients were randomized to receive Epoetin alfa 300 IU/kg (group A, n = 44), 150 IU/kg (group B, n = 42) or no Epoetin alfa (group C). Treatment began 1 day after completion of the monthly chemotherapy cycle, and finished 3 days before initiation of the next cycle, for up to 6 cycles. Reductions in Epoetin alfa dose were made if Hb $\geq$ 15 g/dl. Logistic regression analysis of group C pts showed that low baseline Hb levels or a reduction in Hb level from higher baseline Hb levels, during the first cycle of chemotherapy, were important risk factors for transfusion. Group C required significantly more transfusions than Groups A and B (59%, 21%, 45%, respectively; $P \leq 0.05$). In addition, significantly more pts in group C experienced reduced Hb levels (Hb < 10 g/dl) than those in Groups A and B during cycles 2–5 (66%, 48%, 39%, respectively; $P \leq 0.05$). Epoetin alfa was well tolerated.

In conclusion, Epoetin alfa is effective and well tolerated in preventing anaemia and reducing the risk of transfusion in SCLC pts undergoing cyclic chemotherapy.

235 POSTER

COMPARISON OF TWO STRATEGIES FOR THE TREATMENT OF RADIOGENIC LEUKOPENIA USING G-CSF

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Background: Iatrogenic leukopenia can cause radiotherapy to be delayed or discontinued. This complication can be overcome with the use of granulocyte colony-stimulating factor (G-CSF). However, great uncertainty exists regarding the mode of application of G-CSF in patients treated with radiotherapy. For this reason, the efficacy of two strategies for the administration of G-CSF in irradiated patients was compared in a prospective randomized clinical study. *Material and Methods:* Forty-one patients who developed leukopenia whilst undergoing radiotherapy were treated with G-CSF at a daily dose of 5 μg per kg.. The first group received single injections of G-CSF as and when required (n = 21). The second group received G-CSF on at least 3 consecutive days (n = 20). *Results:* An increase in leucocyte values in the peripheral blood was observed in all patients treated with G-CSF. In the group which received G-CSF when required, two injections (range: 1–8) were administered in most cases. In the second group, most of the patients received 3 injections (range: 3–9). The average duration of therapy interruptions was 4.8 days (0–28) in the first therapy arm and 2.5 (0–20) in the second arm. The variance in the duration of therapy interruptions between the 2 groups was not significant ($P = 0.2$). Radiotherapy had to be terminated in 2 patients due to thrombocytopenia. *Conclusion:* Our results reveal that G-CSF is effective in the treatment of radiogenic leukopenia regardless of the mode of application. The administration of G-CSF on several consecutive days tends to reduce the number of therapy interruptions more effectively than single injections given when required.

236 POSTER

MAP KINASE REGULATION BY PHOSPHATASE 2A IN RESPONSE TO EGF IN A431 CELLS

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EGF is involved in the regulation of cell proliferation in normal as well as in neoplastic tissues. The A431 cells display *in vitro* ambivalent growth properties in response to EGF. We recently demonstrated that the dual effect of EGF is associated to differential mechanisms of p42 MAP Kinase regulation since stimulatory doses of EGF leads to a moderate but persistent activation of MAP Kinase, whereas an abrupt but transitory activation is induced by inhibitory EGF concentrations. In order to clarify the mechanism of MAP Kinase regulation under conditions of positive and negative growth regulation, we have measured the activity of Phosphatase 2A. Our data demonstrate an inverse correlation between PP2A and MAP Kinase activities. Moreover, the addition of 2 nM okadaic acid in A431 cell cultures treated with inhibitory concentrations of EGF inhibits the PP2A activation while restoring MAP Kinase activity.

In conclusion, our data suggest that the activation of MAP Kinase by EGF in A431 cells probably involves the inhibition of PP2A, resulting in an increase of available phosphorylated MAP Kinase

237 POSTER

THE EFFECTIVENESS AND TOLERABILITY OF RECOMBINANT HUMAN ERYTHROPOIETIN (EPOETIN ALFA) IN PATIENTS WITH MULTIPLE MYELOMA REFRACTORY TO CHEMOTHERAPY

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Anaemia is common in patients (pts) with multiple myeloma (MM), and becomes chronic in pts resistant to chemotherapy. This randomized,