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,

parallel, controlled multicentre study evaluated the efficacy and safety of SC Epoetin alfa in reducing anaemia in MM pts refractory to conventional first or second line chemotherapy.

Epoetin alfa (150 IU/kg, 3 times/week initially, increased to a maximum dose of 300 IU/kg 3 times/week) was administered to 40 pts for 6 months. Thirty-one pts were entered into a non-treated control group. Chemotherapy continued during the study in both groups. A response was defined as the discontinuation of transfusion in transfusion-dependent pts (had received $\geq$2 transfusions in previous month) and an increase in Hb $\geq$ 2 g/dl in pts not transfusion-dependent. Overall, significantly more pts responded to treatment in the Epoetin alfa group (75% vs 21%, $P < 0.001$). In the 27 pre-transfused pts (11 controls, 16 Epoetin alfa) there was a trend towards reduced transfusional need in the Epoetin alfa group. In the 44 pts (20 controls, 24 Epoetin alfa) who were not pre-transfused, the mean Hb increase was significantly greater following Epoetin alfa treatment (+2.1 vs −0.2 g/dl, $P = 0.0001$). Increases in hematocrit and red blood cells were also significantly greater in Epoetin alfa-treated pts ($P = 0.0001$) and transfusion requirements were reduced (25% of Epoetin alfa-treated pts vs 45% of control pts). Epoetin alfa was well tolerated. In conclusion, in anaemic MM pts resistant to chemotherapy, Epoetin alfa is a well-tolerated treatment which significantly increases Hb levels in pts regardless of previous transfusions, and reduces transfusional needs in pts who have not received prior transfusions.

238 POSTER

CELL KINETICS OF HEMATOPOIETIC PROGENITORS FOLLOWING CHEMOTHERAPY (CT) PLUS COLONY-STIMULATING FACTORS (CSF'S) IN ADVANCED BREAST CANCER

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Appropriate timing of CSF's administration relative to CT is an important concern in trying to achieve the more effective myeloprotecion. Thirty patients with advanced breast cancer were treated with an intensified FEC regimen, planned at 21 days interval (5-FU 600 mg/sqm + Epirubicin 100 mg/sqm + CTX 750 mg/sqm, on day 1) sequenced with GM- (15 patients) or G-CSF (15 patients) both at 5 u/Kg/day, from day 3 to day 10. Using flow cytometry (FCM) we evaluated the proliferation kinetics of immunomagnetically selected CD34+ BM hematopoietic progenitors before CT and at different times after CSF's stopping. Both the sequence of FEC + GM- and FEC + G-CSF induced a rapid and sustained increase in both the percentage of BM myeloid precursors (BMMP%) and in the cycling status of CD34+ BM cells. However, while the BMMP% remained elevated in both cases after CSF's stopping, the enhanced proliferative activity of CD34+ cells decreased more rapidly after GM-CSF. The early administration of CSF's following CT increases the proliferative activity of CD34+ cells and makes myeloid BM hyperplastic, and this is effective in avoiding peripheral cytopenia. After CSF's stopping, the CD34+ cells proliferative activity subsided leading to a kinetic refractoriness of hemopoietic progenitors more evident after GM-CSF than following G-CSF. These data can be of value for a biologically drived optimal sequencing of CT and CSFs.

239 POSTER

PREVENTION OF ANAEMIA IN CANCER PATIENTS TREATED WITH CISPLATIN-CONTAINING CHEMOTHERAPY

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Cancer patients receiving cisplatin-containing chemotherapy frequently develop anaemia. This open-label, controlled multicentre study tested the safety and efficacy of Epoetin alfa treatment in the prevention of anaemia in patients (pts) with advanced cancer, receiving moderate-high doses of cisplatin (DDP)-containing chemotherapy. Three hundred pts with Hb levels $\geq$ 10 g/dl were randomized to receive either SC Epoetin alfa (150 IU/kg, 3 ×/week), starting on the first day of chemotherapy, and continuing for at least 12 weeks during at least 3 cycles of DDP, or no Epoetin alfa (control). One hundred and sixty-eight pts (82 in Epoetin alfa-treated group, 86 in control group) were fully evaluable (ie completed 3 cycles of DDP and had sufficient haematological data). The groups were divided into 4 sub-groups according to category of neoplasia; lung, ovary, head and neck, other. Baseline and demographic values were similar in both study groups.

The final Hb values were significantly higher in the Epoetin alfa-treated group (13.01 g/dl for Epoetin alfa group, 11.20 g/dl for control group; $P = 0.0001$) and in each of the four Epoetin alfa-treated sub-groups compared to the control sub-groups. Significantly fewer pts in the Epoetin alfa-treated group experienced the development or worsening of anaemia (final Hb < 10 g/dl) (9.8% of Epoetin Alfa-treated group vs 23.3% controls; $P = 0.02$). Six pts in each group received a red cell transfusion. Adverse effects were detected in 8.3% of the Epoetin alfa-treated group, approximately half attributable to Epoetin alfa.

In conclusion, Epoetin alfa 150 IU/kg (administered 3 ×/week) safely maintained Hb levels and significantly reduced the incidence of anaemia in patients with neoplasias, regardless of tumour type.

240 POSTER

IMMUNOHISTOCHEMICAL EVIDENCE OF CYTOPLASMIC AND INTERSTITIAL TRANSFORMING GROWTH FACTOR β3 (TGF β) IN MYELOPROLIFERATIVE DISEASES (MPD)

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TGFβ is known to be involved in the pathogenesis of idiopathic pulmonary fibrosis and liver fibrosis, which is reversible after anti-TGFβ therapy. In bone marrow biopsies (bmb) an increased number of TGFβ positive sinus in M3 leukemia is known (Raza 93). We were interested to look for a correlation of TGFβ positive interstitial structures and b.m. fibrosis. Bmb were dissolved in histocon and frozen with butan methanol in N2. In indirect immuno-alkaline-phosphatase TGFβ and CD61 were stained with mo-ab supplied by Oncogene and Dakopatts. We performed a quantitative evaluation of TGFβ and CD 61 positive cells and a qualitative examination of TGFβ positive interstitial structures according to density in a score of 0–5 similarly to Raza.

Bmb of 10 patients (pts) with MPD at the Hannover classification were evaluated: CML 4 pts (CT No 1, 3; MI No 2, 4); Megakaryoblastic 2 pts (No 5, 6); PTH 1 pt (No 7): MFS 1 pt (No 8 by CMGM): OMS 2 pts (No 9, 10). Fibrosis was strong (grade III) in pts No 8 to 10, minimal (grade I) in pts No 2 and 5 and none in all other pts. The number of CD 61 positive megakaryocytes was higher than the number of TGFβ positive cells in all cases (41.3 vs 28.1 cells/mm^2). TGFβ was strongly increased (Score 4, 5) in pts with a high number of immature megakaryocytes (No 5, 6), and minimal or none fibrosis was seen. TGFβ was moderate (score 3) in MFS (No 8) and minimal or none in all other pts. *In conclusion:* no correlation exists between the degree of fibrosis and TGFβ, and the highest expression of TGFβ was shown in cases with high content of immature megakaryocytes and none or minimal fibrosis.

241 POSTER

A MULTI-INSTITUTIONAL RANDOMISED STUDY ON THE EFFECTIVE SCHEDULE OF LENOGRASTIM ADMINISTRATION IN PEDIATRIC CANCER PATIENTS

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[Objective] A multi-institutional randomised study was performed to compare 1-hour and 24-hour intravenous drip infusion in order to determine the effective schedule of lenograstim (rhG-CSF) for treatment of neutropenia associated with chemotherapy of malignant tumours in paediatric patients. *[Subjects and Methods]* Paediatric patients with lymphoid tumours who are supposed to receive high dose Ara-C were divided into two groups, 1-hour and 24-hour intravenous drip infusion of rhG-CSF 5 μg/kg on post-chemotherapy day 1. Solid tumour patients receiving A1 or new A1 protocol of chemotherapy were divided into 4 groups, 1-hour and 24-hour intravenous drip infusion of rhG-CSF on day 1 or day 4, respective. *[Results and Discussion]* Comparison of 24-hour and 1-hour intravenous drip infusion of rhG-CSF showed that the recovery of neutrophils was quicker and the duration of rhG-CSF administration was shorter in 24-hour continuous intravenous administration. In patients with solid tumour, the nadir value of neutrophil count was higher and the duration of neutrophil count less than 200/μl was shorter in day 1 group when compared with day 4 group. These data suggest that continuous and earlier administration of rhG-CSF is more effective in our setting.