(4 variants) and influenza matrix protein as a control peptide. Patients' pre-vaccine PBL were stimulated *in vitro* with each single peptide. Peptide pulsed T2 cells (Cr^{51} labelled) served as targets for testing CTL activity *in vitro*. *Results:* Patient NW 1 showed a strong CTL response (65% lysins) against the influenza control peptide. A moderate DTH after influenza peptide injection was observed. Patient NW 2 showed a spontaneous CTL activity (41% lysis) against Tyrosinase and Influenza peptide (43% lysis). A clear DTH was observed after Tyrosinase injection. Patient NW 3 showed only minor CTL activity against gp100 (18% lysis) and Influenza peptide (23% lysis) pre-vaccine *in vitro*. A mild DTH was observed after gp100 injection. None of the patients showed detectable changes at tumor sites. No toxic side effects were observed. DTH reactions were only observed for peptides against which a measurable pre-vaccine CTL activity was detected. *Conclusion:* Intradermal injection of nona- or decapeptides showed no detectable toxicity and may induce a measurable immuneresponse *in vivo* without the use of adjuvants.

223 POSTER

INCREASED THYMIDYLATE SYNTHASE GENE EXPRESSION IN METASTATIC MELANOMA

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Thymidylate synthase (TS) is essential for the *de novo* synthesis of thymidylate, a precursor of DNA. It is also a key target for cancer chemotherapeutic agents. We investigated TS expression by semiquantitative reverse transcriptase-PCR in metastatic melanoma, and compared results with those obtained from control tissues. For quantification digital autoradiography was developed. The relative expressions of TS (TS/β-actin) were 0.49, 0.90, 0.44, 0.30, 0.28, 0.36 and 0.54 (mean 0.47) in skin, lymph node, spleen, muscle, gut, and muscle, respectively. In melanoma samples, expression levels varied from 0.85 to 2.6 (mean 2.0). There was no clear correlation between the high TS/β-actin ratio and the fraction size in S-phase. We observed that there was a large variation in TS gene expression in melanoma samples, and that the expression was considerably higher in melanomas than in control tissues. Our data suggests that clinical trials with new thymidylate synthase inhibitors should be taken for consideration in the management of melanoma.

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224 POSTER

COMPARISON OF EFFICACY TWO DIFFERENT DOSE DTIC-BASED CHEMOTHERAPY REGIMENS AND TWO NON-DTIC BASED REGIMENS IN THE TREATMENT OF METASTATIC MALIGNANT MELANOMA; STUDY IN 159 PATIENTS

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159 patients with disseminated malignant melanoma entered the four arm randomized study. Arm A: Adriamycin ADM 40 mg/m^2 day 1, BCNU 120 mg/m^2 and Vincristin (VCR) 1.4 mg/m^2 day 2, DTIC 300 mg/m^2 days 3–6 and Procarbazine (PCB) 100 mg/m^2 days 1–10. Arm B: ADM 40 mg/m^2 day 1, BCNU 120 mg/m^2 and VCR 1.4 mg/m^2 day 2, DTIC 600 mg/m^2 days 3–6 and PCB 100 mg/m^2 days 1–10. Arm C: Vindesine 3 mg/m^2 day 1, Bleomycin 7 mg/m^2 days 1–4 and Cisplatin 30 mg/m^2 days 5–8. Arm D: BCNU 120 mg/m^2 day 1, PCB 100 mg/m^2 days 1–10 and BCG scarification days 8 and 10. The number of evaluable/included patients in each arm was: 28/32 in arm A, 28/31 in arm B, 30/38 in arm C, 54/58 in arm D. Overall RR was 10.71% in arm A, 14.29% in arm B, 30% (6.67 CR) in arm C, 12.96% in arm D. RR was statistically higher in arm C. Main toxicity for arm A and B was leukopenia. Thrombocytopenia increased with DTIC dose escalation in arm B. Nausea and vomiting were equal in arms A, B and C. Arm D was without any significant toxicity. Time to progression and median survival (MS) were similar for all groups, respectively: 2.97 months (MS = 4) in arm A, 3.23 months (MS = 4) in arm B, 2.93 months (MS = 5) in arm C and 3.43 months (MS = 4) in arm D. Results suggest that escalation of DTIC dose (arm B) does not improve RR, at the same time hematological toxicity increases. Deletion of DTIC (arm D) did not reduce RR. Combination with Cisplatin (arm D) seems to be more effective but without benefit regarding time to progression and survival.

225 POSTER

THE APPLICATION OF A NEW INFORMATION TECHNOLOGY—MULTIMEDIA—IN THE PRIMARY AND SECONDARY PREVENTION OF MALIGNANT MELANOMA

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The purpose of this project is to use multimedia techniques to increase public knowledge about malignant melanoma and the risk factors for developing the disease, to increase awareness of preventive measures, and to make people more disposed to change their life style habits. The program is also intended to be a source of knowledge and reference for different categories of medical staff.

The program is resident on CD-ROM. Different presentations can be selected for different target groups: (1) Pregnant women and parents with small children; (2) General population; (3) Health care staff. When in use for the public, the monitor is enclosed in a kiosk and equipped with a touch screen.

The multimedia program will be demonstrated and results of an extensive assessment reported.

226 PUBLICATION

LONG TERM QUALITY OF LIFE IN DACARBAZINE-TREATED PATIENTS RECEIVING TROPISETRON PROPHYLAXIS

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Dacarbazine is a highly emetogenic drug leading to severe nausea and emesis in almost every patient in case no antiemetic treatment is given. Ninety patients with melanoma (Karnofsky index $\geqslant$ 70%) received dacarbazine chemotherapy during up to 14 courses of chemotherapy. As antiemetic prophylaxis, 5 or 10 mg tropisetron was given once daily orally. During chemotherapy, the patients filled in diary cards reporting quality of life and general symptoms (well-being, sleep, nervousness, pain, mood, tiredness, food intake).

In spite of treatment with a highly emetogenic drug, most patients rated quality of life good during several courses. General condition did not change significantly during treatment. Furthermore, normal food intake was maintained in most cases. We conclude that antiemetic prophylaxis with tropisetron helps to maintain quality of life and longterm well-being in patients receiving dacarbazine by effectively preventing the most distressing side effects of chemotherapy.

Growth factors

227 ORAL

PRODUCTION OF BASIC FIBROBLAST GROWTH FACTOR BY HUMAN NON SMALL CELL LUNG CANCER CELLS

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Basic fibroblast growth factor (bFGF), a potent angiogenic cytokine, also acts as autocrine growth factor for certain malignant cells. We investigated the production of bFGF in human NSCLC cell lines (primary and metastatic). In 8/10 cell lines bFGF was detected by immunocytochemistry in cytoplasm. Additionally, Western blot analysis confirmed the presence of this protein in cytosol preparations (CP). With ELISA levels of bFGF in CP were in the range of 50–916 pg/mg protein. Specific mRNA for bFGF was demonstrated in 9 out of 10 cell lines by

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