Results: Fever and myalgia due to rINF-α2b controlled with acetaminophen was seen in 86% of the cases. Six complete response and one partial response was achieved. Pruritis significantly improved in 80% of (4/5) the cases. Recombinant interferon alpha had to be discontinued in one patient because of grade 3–4 nephrotoxicity according to WHO criteria. Recombinant interferon alpha therapy significantly improved phlebotomy requirements, MCV values, erythrocyte and platelet counts, pruritis complaints and the degree of splenomegaly.

Conclusion: Recombinant interferon alpha seems to be an effective treatment modality for the myeloproliferation of polycythemia vera and pruritis complaints.

391 PUBLICATION

Antimetastatic activity of viral oncolysates

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Purpose: Antimetastatic activity of oncolysates obtained from cells of melanoma B-16 and treated by attenuated strain of Venezuelan Encephalomyelitis Virus has been studied.

Methods: Experiments were performed on C57 Bl/6 mice. The tumor strain (Melanoma B-16) was inoculated to animals. The primary tumor was removed 10 days after inoculation and postoperative immunotherapy using viral oncolysate was performed 14 days after inoculation. On days 24–26 metastases in lungs were calculated.

Results: There was found the increase in the index of metastatic spread inhibition from 88 to 100% depending on the schedule of oncolysate administering.

Conclusion: The possible mechanism of this therapeutic effect and its potential for clinical application are discussed.

Hematological malignancies and high-dose chemotherapy

392 ORAL

An in vivo model for multiple myeloma

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The growth of malignant plasma cells in vitro is regulated by cytokines of the IL-6-family and IL-6 itself has been shown to be an important growth factor in vivo. Our aim was to develop a preclinical tumor model for human multiple myeloma. Therefore, the two plasma cell lines JK-6 and the IL-6-dependent INA-6 line were injected into irradiated SCID mice subcutaneously (sc), intraperitoneally (ip) or intravenously (iv). Some animals received recombinant human IL-6 (1 μg, ip, twice a week) (kindly provided by Sandoz). JK-6 grew as sc, ip or iv tumor with infiltration of spleen, liver, and bone marrow. In some cases, plasma cells were detected in blood smears. IL-6-dependent INA-6 cells gave rise to ip tumors which, in contrast to JK-6, led to development of ascites in these mice around day 80 to 90. Surprisingly, these INA-6 xenografts did not require IL-6 injection for proliferation in SCID mice, however when recultured in vitro after excision were strictly IL-6-dependent again. As mouse IL-6 is known not to act on human cells, the role of other cytokines of the gp130 family is currently under study. To our knowledge, this is the first xenograft tumor model for multiple myeloma with an IL-6 dependent human cell line, allowing to study growth regulation by cytokines in vivo. New therapeutic strategies including immunotherapy may be studied in this unique tumor model.

393 ORAL

Vinorelbine (VRL) in patients with recurrent multiple myeloma (MM): A phase II study

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Vinorelbine, a new semi-synthetic Vinca-alkaloid, is a potentially new alternative in the treatment regimen of MM. 33 patients (15 women, 18 men), aged 55 to 76 (median 66) with stage II–III MM, relapsing after one or two conventional chemotherapies or after one high dose chemotherapy were included. VRL was administered at 20 mg/m2 on D1 and D4 every 21 days in the first cycle. If the tolerance was good, the daily dose was escalated to 25 mg/m2 in the subsequent cycles.

Out of the first 33 patients, 2 patients were ineligible, 1 patient died after one cycle of treatment with a background of aortic insufficiency. 5 patients were non-evaluable, 2 developed a cardiac toxicity after a long-standing heart disease, and 1 a severe acute sepsis. Patients received a total of 148 cycles (1–18 cycles, median 3 cycles). The mean dose-intensity on 138 cycles (D1 and D4) of VRL was 21.64 mg/m2. From 22 evaluable patients for efficacy, 5 had a partial response (PR), and 2 a minor response (MR). 9 patients were stabilized and 6 progressed. The overall response was 33% (IC 95: 12–52%), and in intention to treat analysis 21% (IC 95:7–35%). The median time to progression among the 33 patients was 119 days (10–809). Toxicity was mainly hematologic, with grade 3–4 neutropenia mainly (cycles 1 and 2). There was no major toxicity on platelets or hemoglobin. There was one infection without grade 4 neutropenia. Non hematologic toxicity was observed very rarely (one grade 4 vomiting and diarrhea, no neurologic constipation).

Our results are comparable to those obtained with high dose dexamethasone (Alexanian et al, 1986). In summary, these preliminary data show that VRL monotherapy is active in recurrent MM. A phase II study combining VRL + dexamethasone is currently underway in relapsed MM patients.

394 ORAL

A placebo-controlled study of epoetin alfa in multiple myeloma (MM) patients with anaemia

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Purpose: This international, multi-centre, double-blind study evaluates the effect of treatment with epoetin alfa (EPO) or placebo on transfusion need and severity of anaemia in MM patients undergoing chemotherapy (CT).

Methods: 145 MM patients with anaemia (haemoglobin < 11.0 g/dL), who had received at least 6 months of CT, were stratified according to pre-study transfusion need and randomised 1:1 to EPO (150 IU/kg 3 × week, SC) or placebo, with a possible dose increase after 4 weeks depending on the haemoglobin (Hb) response. The study consisted of a 12 week double blind phase, followed by an optional 12 week open label phase (not reported here).

Results: 28% of EPO treated patients required transfusions during study months 2 or 3 versus 47% of placebo treated patients ($p = 0.02$, Fisher's exact test, "intention to treat" population). There was no significant difference between the treatment groups in the proportions of patients with pre-study transfusions (36% and 37%, $p = 1.00$, Fisher's exact test). Time to first transfusion after at least 1 month on-study was prolonged in the EPO treatment group ($p = 0.05$, log-rank test). The proportions of Correctors (achieved Hb ≥ 12 g/dL) and Responders (Hb increased ≥2 g/dL above baseline) were higher in the EPO group (38% and 47%) than in the placebo group (3% and 5%, $p < 0.001$, Fisher's exact test, efficacy population).

Conclusion: Treatment with EPO is effective in reducing transfusion need and correction of anaemia in MM patients undergoing cytotoxic CT.

395 ORAL

Cladribine (CdA) therapy in chronic lymphocytic leukemia (CLL) – Long-term follow-up of 117 patients

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CdA is effective therapy for CLL. We have treated 117 patients with symptoms with CdA in 5-day monthly courses. Previously treated patients had 0.12 mg/kg/day in 2 hour iv infusions (n = 53), and untreated patients had the corresponding dose 10 mg/sqm/day orally (n = 64). There were 56 patients in Binet stage C (48%), 22 in stage A (19%) and 39 in stage B (33%). Median age was 62 years (range 38–88 yrs), and the median lymphocyte count was 70 × 10 (9)/l (range 5–460). CR rate according to NCI criteria was 35%, and 32% had PR. Response rate was correlated to Binet stage ($p = 0.007$) and to number of previous regimes ($p = 0.025$), with a 41% CR rate among those with one or no previous regime. Fifty-nine patients (50%) have died, with a median survival of 20.5 months. The median observation time of surviving patients is 3 years (range 18–71 months). The three-year and median survival of patients who achieved CR (n = 41) are 82% and 5.7 years, PR (n = 38) 63% and 3.3 yrs, and NR (n = 38) 13% and 0.9 yrs. Previously untreated patients (n = 64) had a 3-yr survival of 68% (median not

reached), and corresponding figures for those with 1–2 previous regimes were 50% and 3 yrs, and ≥3 previous regimes 13% and 0.8 yrs.

Responding patients may achieve a prolonged remission and survival, but response is less likely in heavily pretreated patients.

396 ORAL

The role of lung function measurements before allogenic BMT to anticipate long term lung failure

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Background: Lung function often deteriorates after allogenic BMT for hematological malignancies, and lung failure is the most important cause of death after grafting. To test whether pre-BMT lung function impairment is associated with long term lung deterioration, we prospectively measured lung function parameter of 80 consecutive patients with AML (n = 23), CML (n = 38) and ALL (n = 19) before allogenic BMT, after 6 months, and thereafter annually until 5 years after grafting.

Results: Pretransplant forced expiratory volume in one second (FEV1), diffusing capacity for carbon monoxide (TLco) and vital capacity (VC) were significantly decreased in the ALL subgroup (FEV1 85% pred, TLco 79% pred, VC 83% pred, ECCS normal values). In contrast, no pre-BMT lung impairment was detectable in CML and AML patients. During the first 6 months after BMT lung function parameter decreases in all patient groups in a similar way (FEV1 15 ± 7.3%, TLco 23 ± 11.2%, VC 19 ± 9.8%). Further, all lung parameter at least partially recovered within one year. Long-term decline in FEV1, TLco and VC happened in all patients groups without significant differences. No association was detectable between pre-BMT, 6 months after BMT and long term lung function decrease.

Conclusion: Pretransplant lung function impairment is not associated with increased relative risk for long term lung failure in allogenic BMT patients.

397 ORAL

Platelet recovery after high-dose (HD) chemotherapy (C) is superior with peripheral blood stem cells (PBSC) mobilized by C + G-CSF compared to G-CSF alone

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Collection of PBSC mobilized with G-CSF is often more predictable and easier to perform than mobilization using C. We evaluated two mobilization strategies to support women receiving cyclophosphamide 6 g/m^2, mitoxantrone 64 mg/m^2, carboplatin 0.8–2.0 g/m^2 over 4 days (d) for C-sensitive metastatic breast cancer. 35 consecutive pts received FAC (cyclo 2 g/m^2) d1 + G-CSF 10 μg/kg d4–14, with leukapheresis (10–12 L) × 4 d12–15 (C + G, n = 16); or G-CSF 10 μg/kg d1–7 with leukapheresis d5.6 ± 7.8, depending on CD34 recovery (target > 2 × 10^6/kg) (G, n = 19). Number of collections/pt: C + G 3:2pts, 4:12, 5:2; G 2:5 pts, 3:5, 4:8, 5:1. CD34+ cell recovery (× 10^6/kg) was greater for C + G: median 12.9 vs 3.5 (p = 0.009), whereas CFU-GM, total cell number were similar. Mean D to ANC > 0.5 × 10^9/L were similar (C + G: 10.9, G: 12.4, p = 0.15), but mean d to plts > 20 × 10^9/L was less for pts collected after C + G (12.8 vs 24.4, p = 0.03). Plt recovery and time to hospital discharge (DC) were significantly shorter for C + G pts (logrank p = 0.02 and 0.001 respectively), with similar ANC recovery (p = 0.14). Prior adjuvant C did not affect apheresis yield, engraftment or time to DC. For women receiving HDC for MBC, PBSC mobilized with C + G may be superior to G alone, at least with respect to plt recovery.

398 ORAL

Treatment of patients with relapsed or refractory acute myeloid leukemia (AML) with recombinant engineered human anti-CD33 antibody-calicheamicin drug conjugate

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CMA-676 is a conjugate of the potent cytotoxic agent calicheamicin linked to a recombinant engineered human antibody directed against the CD33 antigen, which is commonly expressed on AML blast cells. The lack of CD33 antigen expression on hematopoietic stem cells allows for selective delivery of the cytotoxic calicheamicin to the tumor target, while sparing normal stem cells. Patients with CD33-positive relapsed or refractory AML received CMA-676 as a single 2-hour IV infusion per treatment cycle every 14 days for up to 3 cycles at the same dose, contingent upon a lack of leukemic progression and significant toxicity. Three to 6 patients were treated at escalating dose levels of CMA-676. Between April 1995 and December 1996, 36 patients from 23 to 73 years of age, were entered. CMA-676 was well-tolerated at all dose levels. Fever and chills occurred in 26 (74%) patients. Three patients experienced Grade III hepatic toxicity. Dose-limiting toxicity was not observed, and only one patient discontinued the study due to fever and hypotension. Marrow morphologic remissions were achieved in 5 patients, two of whom recovered normal blood counts for 6 months before experiencing relapse. Three other patients achieved morphologic remission; however one died of fungal sepsis, one remained transfusion dependent in morphologic remission for 70 days when bone marrow relapse occurred, and one experienced CNS relapse after a morphologic remission of 40 days. We conclude that single-agent therapy with CMA-676 safely induces remission in some patients with relapsed or refractory AML.

399 ORAL

Transplant-related morbidity (TRM) in patients undergoing bone marrow transplantation (BMT): The role of preparative regimens (PR)

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Purpose: This retrospective analysis evaluated acute and late toxicities after BMT according to PR.

Methods and Materials: From January 1984 to December 1994, 229 patients with acute leukemia (AL, n = 114), chronic myelogenous leukemia (CML, n = 53), lymphoma (51) and aplastic anemia (11) were transplanted (171 allogeneic BMT, 58 autologous BMT). Preparative regimens were combining cytotoxic drugs (cyclophosphamide) with TBI (TBI group, n = 146) or without TBI (cyclophospamide, busulfan) (CHE group, n = 83). Median age was 32.4 years. Median follow-up was 36 months (0.3–121).

Results: There was no difference in term of white blood cell count recovery, engraftment, veno-occlusive disease and hemorrhagic cystitis between the 2 groups. The CHE group presented an increased incidence of second malignancies. The TBI group showed an higher incidence of platelets and red blood cell transfusion, cataracts (especially with cobalt irradiation), aseptic necrosis of bone and interstitial pneumonitis (IP). IP occurred in 25% of TBI group, especially in patients with graft-vs-host disease. Survival according to the type of preparative regimens was similar (Cox model). According to the BMT type, survival was better with allogeneic BMT even if TRM was higher in this group (especially with TBI, 73% vs 12%).

Conclusion: Although patients treated with TBI experienced more late toxicity, survival remains the same. This could be explained by the higher rate of relapses in the CHE group. Therefore TBI keeps its place as first intent treatment choice.

400 POSTER

Development of a "myeloma risk score" for patients with a paraproteinaemia

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Purpose: Diagnostic systems for monoclonal gammopathies use bone marrow and X-ray examinations to exclude multiple myeloma (MM). Data from a population-based registry of unselected patients with paraproteinaemia indicate that these tests are frequently not performed. We therefore evaluated the possibility of estimating the risk for MM in patients with paraproteinaemia using only standard laboratory tests.

Methods: We used 441 randomly selected patients to develop a simple four point "Myeloma Risk Score" based only on paraprotein type and concentration. One point was given for concentrations ≥10 g/l, one point for IgG and IgA, and two points for IgD and light chains only. A score of 0 or 1 indicated a low risk for MM, with scores of 2 and 3 signifying high risks.

Results: Sensitivity, specificity, positive and negative predictive value (PV) for the Myeloma Risk Score in the training sample were 92%, 88%,