stage III whereas 43% had serous and 25% mucinous adenocarcinoma. 30% of patients had an optimal operation with residual disease (RD) ≤ 1 cm. All patients received carboplatin AUC 7.5 1 h infusion q 3 wks for a maximum 6 cycles. GM-CSF was also given 5 mcg/kgr days 2–14 of each cycle. 44 (53%) women entered cCR and 17 (20%) cPR. 21 women out of 44 with cCR were randomized to receive IP IFN and 23 for follow-up without treatment. IFN was given IP through catheter 25 × 10^6 units q 2 wks for 12 doses. 12 (57%) patients of the IFN group are still alive with a median survival 41.64 (15.90–52.16) months whereas 14 (60%) of the control group are alive and the median survival has not been reached (P = 0.46). In the subgroup of RD ≤ 1 cm the median survival of the patients with IFN has not been reached whereas in the control group is 25.90 (19.38–51.38) months (P = 0.28). Fever grade 3 (9%) was the main toxicity of IFN whereas thrombocytopenia grade 3–4 11%–24% was for Carboplatin without toxic deaths. We conclude that IP IFN consolidation in cCR OC patients following Carboplatin CT in feasible, tolerable without survival advantage

386 POSTER

Epithelial cells in the bone marrow (BM) of colorectal carcinoma (CRC) patients: A tool to monitor immunotherapy?

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Purpose: Immunotherapy is effective as adjuvant treatment for CRC pts. The therapeutic effect in advanced disease is limited. The development of adjuvant therapy requires a large number of pts and a long follow-up period. Surrogate end-points might therefore aid in the evaluation of a new therapeutic approach. However, new treatment concepts are mostly evaluated primarily in advanced disease where a clinical effect might not frequently be seen. The presence of cytokeratin positive (CK+) epithelial cells in BM of pts with CRC correlates strongly to the prognosis. Analyses of such cells during immunotherapy might be a way to early evaluate the therapy.

Methods: A double immunohistochemistry technique has been developed and used on BM aspirate (BMA) from 47 CRC pts with advanced disease or treated in the adjuvant setting. The pts received various combinations of unconjugated MAb17-1A.

Results: The presence of CK+ cells were found in 20/42 (48%) pts BMA. In further 5 pts the BMA was inadequate. p53 was detected in the nucleus of CK+ cells in 11/20 pts. KI 67 was seen in CK+ cells in 9/20 pts. CK+ cells were noted in aggregates in 12/42 pts. In 6 pts analyses showed CK+ cells in BMA before but not after treatment. In one pt this was paralleled by clinical tumor response.

Conclusions: Routinely processed BMA can be used to evaluate CK+ cells in the BM. Preliminary results indicate that CK+ cells in BM might be used to monitor immunotherapy.

387 PUBLICATION

Adjuvant therapy of renal cell carcinoma (RCC) with a pure cell-lysate autologous tumorvaccine (aTm)

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Purpose: An adjuvant therapy for RCC after radical tumor nephrectomy is not available. Therefore we investigated for this indication the efficacy of a pure cell-lysate autologous tumorvaccine produced by macropharm GmbH (autologous-tumorvaccine-macropharm, aTm).

Methods: 169 patients with RCC have been treated with aTm after radical tumor nephrectomy. The progressive free survival probability of these patients was compared to a historical control group of 107 patients from the same hospital, which received identical surgical treatment but without any adjuvant therapy.

Results: According to identical in- and exclusion criteria and two independent biometrical analyses there was no statistical difference between the main epidemiological and clinical parameter of the two patient groups. As a consequence, any observed significant effects resulting from the treatment with aTm are based on assumptions to be most probably clinically relevant. Two years after nephrectomy, the first analyses provide evidence that there exists a difference of 22.8% in favor of the aTm group (pT2, 3a, 3b pNO/+ MO). Only two patients out of 169 (aTm-group) showed minor side effects not exceeding WHO-grade I.

Conclusion: The results presented here justify a prospective randomized controlled and multicenter phase III study, which is underway now.

388 PUBLICATION

Interleukin-2 (IL-2), interferon-α (IFN-α), 5-fluorouracil (5-FU) and vinblastine (VBL) for metastatic renal cell carcinoma (MRCC): A clinical and immunological study

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Patients: 12 pts, 7 males and 5 females, median age 62 with MRCC in lungs, bones, liver, lymph nodes or contralateral kidney were included in this study. 11 pts had previous nephrectomy with DFS of 0–200 mos.

Treatment: IL-2 10 MIU/m2, S.C., 3 ×/week, weeks 1–4, IFN-α 6 MIU/m2, S.C., 1 ×/week, weeks 1–4 and 10 MIU/m2, 3 ×/week, weeks 5–8, 5-FU 600 mg/m2 and VBL 6 mg/m2, I.V. bolus, weeks 5 and 7. Courses given every 2 weeks.

Results: 11 pts were evaluated for response and toxicity. CR: 2 pts (+10, +6 mos), PR: 3 pts (+3, +3, +10 mos), SD. 2 pts and PD: 3 pts. Treatment was stopped in 1 patient due to toxicity. Mean values of T-cells phenotypings before treatment compared to normal: CD3 73% ± 8.8 vs 66% ± 8.8 ($p < 0.002$), CD4/CD8 1.1 vs 1.5 (1.6 after treatment), CD69 CD4 21% ± 10.3 vs 40% ± 13.0 ($p < 0.001$) and 37% ± 16.1 after treatment ($p < 0.05$). sIL-2R 1,919 vs 500 u/ml ($p < 0.001$). Side effects were flu-like syndrome, nausea, vomiting and depression.

Conclusion: This treatment schedule is effective, safe with acceptable toxicity. The study is still ongoing, to confirm these clinical results.

389 PUBLICATION

Targeted delivery of esperamicine A1 by using oncofetal protein α-fetoprotein

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Purpose: Human oncofetal protein α-fetoprotein (AFP) was selected as a vector for tumor specific delivery of esperamicin A1 (Esp) to the target cells due to the overexpression of AFP-receptors on the surface of malignant cells. Because of the very high toxicity of free Esp it's possible to use the conjugate AFP-Esp in extremely low concentrations of AFP. The aim of this work was the study of antitumor activity of AFP-Esp conjugates.

Methods: The method used for Esp conjugation with AFP involved AFP thiolation by SPDP after reducing the S-S bonds with dithiothreitol. The therapeutic activity of AFP-Esp was estimated taking the increase in mean life-span (ILS) and the tumor size of treated animals as a criteria.

Results: The free Esp was about three times more toxic than it's conjugate with AFP for different human and mouse tumor cell lines in vitro. In vivo in the model experiments on DBA/2 mice with inoculated s.c. P388 tumor the ILS for treated by the conjugate mice was about 120% for two months period. 92% of treated animals didn't develop tumors and were alive over 6 months.

Conclusion: Conjugates of AFP with Esp possess a very high therapeutic activity against solid tumors in mice. The rationality of using AFP conjugates with antitumor drugs for the development of new chemotherapeutic approaches for cancer treatment is discussed.

390 PUBLICATION

The efficacy of interferon alpha in polycythemia vera

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Purpose: In chronic granulocyte leukemia (CGL), primary thrombocytosis and idiopathic myelofibrosis recombinant interferon alpha (rINF-α) used as myelosuppressive agent. Recently, there is some reports about the use of rINF-α in polycythemia vera (PV).

Methods: In our study therapeutic efficacy of rINF-α has been evaluated in 7 (6 male 1 female) patients with PV, diagnosed according to the criteria of Polycythemia Vera Study Group. Patients follow up was 5 years. Recombinant interferon-alpha 2b was started as 3 mU 3 times a week sc.

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