micellar (Paclical® Oasmia Pharmaceutical, Uppsala, Sweden) is a novel cremophor-free formulation of paclitaxel using retinoyl derivatives as surfactant. The purpose of the study was to determine the maximum tolerated dose and pharmacokinetics of the study drug in patients with recurrent solid tumours.
Materials and Methods: Freeze-dried micellar paclitaxel, dissolved in Ringer-Acetate, was given as a one-hour IV infusion in doses from 90 to 275 mg/m^2 without premedication to patients with recurrent solid tumours where no standard treatment was available. Treatment was repeated every 21 days for 3 cycles. A pharmacokinetic evaluation was performed.
Results: Thirty-four patients received the study drug. Dose-limiting (grade 3) peripheral neuropathia, intestinal obstruction and fatigue was observed at 275 mg/m^2 in three patients of six. Twenty-nine cycles were administered at 250 mg/m^2, with two cases of neuropathy grade 3 one of whom also experienced a stomatitis and neutropenic fever grade 3. Other side effects (grade 1−2) included alopecia, transient loss of appetite, mucosit, fever and fatigue. No hypersensitivity reactions were observed. Pharmacokinetic evaluation revealed a fast tissue distribution of paclitaxel, with an α-T1/2 of 30 minutes, and a distribution being completed in 2 h. The Vss was of the order of 57 L/m^2. Clearance ranged from 4.4 to 22.6 L/h/m^2 (median 11.9). The elimination half-life, which to a large extent is dependent on clearance, ranged from 4.8 h to 23.1 h.
Conclusions: Paclitaxel, micellar (Paclical®) can be administered in 60 minutes without premedication and appears to be safe at a dose of 250 mg/m^2 despite the fact that the study subjects were heavily pretreated. Pharmacokinetics shows a rapid distribution of the order of 0.5 hours. The tissue distribution is extensive according to the large Vss, of the order of 57 L/m^2.

730 POSTER

Novel water-soluble Ag-metalloporphyrins as potential chemotherapeutics: analysis of structure–activity relationship

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Background: Porphyrinic compounds are extensively studied as a perspective new class of chemotherapeutics. They are known to accumulate selectively in tumor tissues. In the present work the properties of novel metalloporphyrins as potential chemotherapeutics were studied.
Materials and Methods: The initial porphyrin (meso-tetra(4-N-pyridyl)-porphine) was synthesized by the modified Adler method. The new water-soluble cationic porphyrins with various functional groups (allyl, butyl, oxyethyl, metallyl) and their metal (Zn, Ag, Co, Fe) derivatives were developed. To increase in the availability of new porphyrins for cells and tissues a molecule trinitrate 5-mono-(3-methoxy-4-hexadecyloxyphenyl)-10,15,20-tri-(4-N-allylpyridyl)porphinato Ag(II) bearing lipophylic group was also synthesized. The structure and purity of synthesized compounds were determined by TLC, NMR (Mercury Varian 300), and electronic absorption spectroscopy (Perkin-Elmer Lambda 800). The cytotoxicity of synthesized porphyrins were evaluated in vitro (human chronic myeloid leukemia cells, line KCL22) by trypan blue exclusion test.
Results: Ag-derivative of meso-tetra(4-N-allylpyridyl)porphine (TAll4PyP) was shown to be more cytotoxic than TAll4PyP and its Zn-, Co-, and Fe-complexes. It was also more toxic than known chemotherapeutics cis-platinum and cyclophosphamide. The Ag-porphyrins bearing various functional groups were found to arrange by their toxicity in the following order: Ag-TAll4PyP $\approx$ Ag-TMetAllyl4PyP > Ag-TButyl4PyP > Ag-TOxyethyl4PyP. The making of the porphyrin molecule more lipophylic (amphiphylic) led to the increment of its cytotoxicity and the decrease in IC50 (concentration inducing 50% inhibition of cell viability) value.
Conclusions: The structure-activity relationship analysis of new porphyrins has revealed that:

i. The cytotoxicity of porphyrins is due to presence of a central metal atom in porphine ring and varies depending on metal. Ag-derivatives of new porphyrins were more cytotoxic than Zn-, Co-, and Fe-metallocomplexes.
ii. The porphyrins bearing in their structure allyl-functional group were evidenced to be more cytotoxic than those including butyl-, oxyethyl-, and metallyl-groups.
iii. Porphyrin including a lipophylic group seems to be more effective than hydrophylic ones.

The results obtained can be useful for further design of new porphyrins as potential chemotherapeutics.
This work was supported by the NFSAT (GRASP 29/06).

731 POSTER

Open-label, single-dose, phase I study evaluating the mass balance and pharmacokinetics (PKs) of sunitinib (SU) in healthy male subjects

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Background: SU is an oral multitargeted tyrosine kinase inhibitor of VEGFRs, PDGFRs, KIT, RET and FLT3, approved multinationally for the treatment of advanced RCC and imatinib-resistant/-intolerant GIST. In cultured human liver microsomes, SU is primarily metabolized by CYP3A4 to form SU12662, the N-desethyl metabolite. In-vivo rat and monkey studies identified SU12662 as the major metabolite and showed that SU and SU12662 are mainly excreted in feces, with urinary excretion as a minor route of elimination. This study intended to characterize: the primary routes of elimination of SU and drug-related material; PKs of total radioactivity, and plasma SU and SU12662; the metabolites of SU in plasma, urine and/or feces.
Materials and Methods: This open-label, single-dose, single-center study evaluated the mass-balance and PKs of SU in healthy adult male subjects (N = 8). On day 1, each subject received a single oral 50 mg SU capsule containing approximately 100 μCi of [^{14}C]-SU. Serial blood samples were collected at specified times over 21 days. Total urine and fecal collections were taken just before dosing and in 24-hr intervals (urine) and as passed (feces) until the end of the study. Safety/tolerability measures were also recorded.
Results: 6/8 subjects were evaluable for mass-balance evaluation. 77% of the radioactive dose was recovered in feces (61%) or urine (16%) over the 21-day period, mostly within the first 7 days. Total radioactivity recovered in feces was 4-fold greater than in urine. SU and SU12662 were identified in plasma, feces and urine. SU and SU12662 represented 71% and 20.5%, respectively, of total radioactivity in the pooled plasma samples and 41.5% and 44.9%, respectively, in the pooled urine samples. In addition, the N-oxide SU12487 was detected in plasma and urine, and two other minor metabolites were detected in feces. Radioactivity level-time profiles indicated that SU and metabolites showed preferential portioning into erythrocytes over plasma. Plasma PK parameters were consistent with those reported in prior single-dose human studies with non-radiolabeled drug. 5/8 subjects experienced grade 1 AEs that resolved; there were no clinically significant (grade 3/4) AEs.
Conclusions: Fecal excretion was the major route of elimination of SU and its metabolites in this study of healthy human subjects, consistent with results from preclinical studies. The PK profile was consistent with prior reports from phase I studies using non-radiolabeled drug.

732 POSTER

Phase I clinical study of the humanized monoclonal anti-epidermal growth factor receptor (EGFR) antibody (Nimotuzumab) in combination with chemotherapy in patients with locally-advanced breast cancer. Preliminary results

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Background: Epidermal growth factor receptor (EGFR) is overexpressed in 14−91% of breast cancer (BC). Nimotuzumab (hR3) is an IgG1 humanized monoclonal antibody that recognized an epitope located in the extra cellular domain of the human EGFR. Clinical efficacy has been shown in adult with high grade gliomas and head and neck cancer. The phase I study assessed the safety, pharmacokinetics (PK), and efficacy of the combination of Nimotuzumab administered concomitantly with chemotherapy in patients with locally advanced breast cancer tumours in the neoadyuvant setting.
Patients and Methods: Patients with locally advanced BC were recruited to a dose-escalation study of nimotuzumab (weekly doses) at 50, 100, 200 and 400 mg/dose, respectively (3 patients per cohort) followed by doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 every 3 weeks. The PK analysis was the determination of the area under the serum concentration versus time curve (AUC) and the half-life (t 1/2). Pharmacokinetic parameters were estimated after the first and the last antibody infusion.
Results: The maximum planned nimotuzumab dose of 400 mg was achieved without reaching the maximum tolerated dose. Grade 1 non-acneiform skin rash in 10 patients was the most frequent nimotuzumab-related side-effect and only one patient developed acneiform skin rash

(grade 1). Grade 2 toxicities included hyperglycemia (n = 4) and diarrhea (n = 1). There were no relationships between specific toxicity and dose level, and no detectable differences in the incidence or severity of adverse events between the first cycle and subsequent cycles. Partial responses were obtained in nine patients and stable disease in three that required a second line of chemotherapy (taxanes-based regimen) and all patients developed a skin rash during this chemotherapy (without concomitantly administration of nimotuzumab). No antibodies to nimotuzumab were detected. The optimal biological dose has not reached yet. Further dose escalation and analysis of pharmacodynamic is ongoing.
Conclusions: Nimotuzumab administered concomitantly with chemotherapy was safety and well tolerated. No severe adverse reactions were detected and the antibody showed a low immunogenecity. Skin rash was observed for first time after using nimotuzumab in combination with doxorrubicin and cyclophosphamide. The maximum tolerated dose and the optimal biological dose have not reached yet.

733 POSTER

The administration of pegfilgrastim following myeloablative chemotherapy for sufficient peripheral blood stem cell (PBSC) mobilization in patients with solid organ tumors and lymphomas

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Background: The classical methods of peripheral blood progenitor cell mobilization consist of daily administration of filgrastim following myeloablative chemotherapy. New forms of G-CSF with prolonged half life time reduce patients' stress, improve their compliance and possibly contribute to improvement of PBSC mobilization. The aim of the study was to investigate whether sufficient harvesting of cells is achieved with pegfilgrastim as well as to determine the optimal dose.
Materials and Methods: Two groups of patients with solid tumors and lymphomas received either 6 mg or 12 mg of pegfilgrastim, 24 hours following the administration of high dose chemotherapy (cyclophosphamide 4.5 g/m^2 or etoposide 1.2 g/m^2). Daily blood samples for CD34+ cells were obtained after peripheral blood leucocyte recovery following leucocytopenia due to chemotherapy.
Results: Twenty three patients were included in the study and the parameters studied are listed in the table. No statistically significant difference was observed between the two groups for these parameters (p = ns).

Groups	Patient number	Apheresis day, median value (range)	MNC$\times 10^8$/kg, median value (range)	CD34$\times 10^6$/kg, median value (range)	WBC$\times 10^3$/l median value (range)
Group 1 (pegfilgrastim 6 mg)	14	13 (7–18)	2.405 (1.06–6.61)	4.91 (1.22–16.17)	7.2 (4.2–13.4)
Group 2 (pegfilgrastim 12 mg)	9	10 (7–13)	3.91 (1.77–6.45)	5.88 (3.64–34.15)	8.5 (5.4–18.1)

Conclusion: The number of the harvested PBSC's following myeloablative chemotherapy is sufficient after 6mg of pegfilgrastim and comparable to that collected following daily filgrastim, as previously described by our group.

Immunotherapy

Poster presentations (Thu, 27 Sep, 08:00–11:00) Immunotherapy

800 POSTER

MOR202 – a fully human antibody targeting CD38 for the treatment of multiple myeloma and other forms of blood-borne malignancies

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CD38 is a cell surface protein expressed by a variety of hematopoetic cells. Overexpression of CD38 seems to play a key role in various forms of leukaemia and – even more pronounced – in multiple myeloma (MM). To date, MM is an incurable malignancy with a median survival period of three to four years after diagnosis.
Fully human antibodies directed against CD38 were selected by cell panning strategies from the MorphoSys HuCAL GOLD® phage display library. The lead candidate MOR202 was chosen from several antibodies recognizing different epitopes on CD38.
MOR202 was subject to comprehensive in vitro- and in vivo-studies: It displays a low nanomolar affinity to CD38 and recognizes the protein on a wide variety of cancer cell lines as well as on all primary MM patient samples tested in FACS and IHC analysis. In the human IgG1 format, MOR202 is able to kill CD38-positive cell lines and primary MM cells from patients by antibody-dependent cell-mediated cytotoxicity (ADCC) with picomolar EC_{50} values, whereas progenitor cells remain unaffected as shown by a clonogenic assay. Furthermore, MOR202 reduces tumour growth (RPMI8226) in a SCID-mouse model and increases the animals' overall survival rate. The excellent efficacy in the SCID xenograft model was even superior to the effects of Velcade® tested in the same study.
In summary, MOR202 appears to be a promising candidate for the treatment of MM and other CD38-related diseases.

801 POSTER

A strategy for generation of human tumor-specific T cell lines for adoptive transfer in follicular lymphoma patients

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Background: Adoptive T-cell therapy using donor lymphocyte infusions is a promising approach for treating hematological malignancies. But, efficacy is limited by the induction of graft-versus-host disease. Transfer of tumor-specific T-cell lines or clones could enhance the graft-versus-tumor effect and eliminate graft-versus-host disease. However, isolating antigen-specific T-cell lines is a time-consuming and laborious process. We tried to optimize expansion of tumor-specific autologous T-cell lines from patients with follicular lymphoma.
Materials and Methods: Lymphoma-specific T-cell lines were generated by repeated in vitro stimulation of lymphocytes isolated from tumor or blood with autologous soluble CD40 ligand-activated tumor cells. On day −3, tumor cells were obtained from frozen lymphoma sample by CD3 depletion and activated with sCD40L + IL-4 for 72 hours. On day 0, TILs obtained from frozen lymphoma sample by CD19 depletion or CD3 enriched autologous PBMCs were cocultured with activated tumor cells at the ratio of T cell 1 vs. tumor cells 4. Cytokines (IL2 and IL15) were supplemented 48 hrs after starting culture. T cells were harvested on day 10 and restimulated with tumor cells. A total of 4 rounds of stimulations were done. To determine whether the presence or absence of immunostimulatory or immunosuppressive factors in the tumor microenvironment influence the generation and function of lymphoma-specific T cells, the surface expression of co-stimulatory/co-inhibitory molecules (CD40, CD54, CD58, CD80, CD86, PDL1, PDL2, B7H3, B7H4, BTLA, ICOS-L) expression before and after tumor activation with sCD40L + IL-4 was evaluated.
Results: Autologous tumor-reactive T-cell lines were generated in 8/11 follicular lymphoma patients. Two T-cell lines & clones were reactive against native autologous FL cells (Group A). Six T-cell lines & clones didn't show reactivity against native autologous FL cells, but were reactive against sCD40L activated autologous FL cells (Group B). Three T-cell lines & clones did not recognize native or activated tumor cells (Group C). Expression of most co-stimulatory molecules on the tumor cells was comparable between the three different groups before and after activation with sCD40L. But, ICOS-L expression was low in 2/3 patients in whom tumor-reactive T-cell lines could not be generated (Group C).
Conclusions: Tumor-specific T-cell lines could be generated by co-culture with autologous soluble CD40 ligand-activated tumor cells and confirmed to retain specificity against autologous tumor cells in a cytokine induction assay. This approach could be successfully used to isolate lymphoma-specific T-cell lines from follicular lymphoma patients.