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.
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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