> grade 2 occurs. From this DL, the dose will increase with 66%, 50%, 33% and 25% successively. Standard haematological, biological and clinical dose limiting toxicity (DLT) definitions are used. Activity is assessed at the end of every 2nd cycle (cy). PK is determined at d 1 of cy 1.
Results: 11 pts with solid tumours have been included (4 colorectal, 2 hepatocarcinoma and one each of NSCLC, cholangiocarcinoma, leiomyosarcoma, malignant melanoma, pancreas) with 1 pt/DL from 30 to 240 mg/m^2/d. One grade 2 adverse event (AE), neutropenia, was reported at 480 mg/m^2/d. A total of 4 patients were included at this DL. Accrual is ongoing at 800 mg/m^2/d (DL6). One DLT is reported at 800 mg/m^2/d; d 8 treatment postponed with more than 2 weeks due to reduction in Hb and platelets (CTCAE grade 3) after d 1 treatment. A total of 18 cycles (1 to 4/pt) of treatment have been administered. The main treatment-related AEs have been nausea and vomiting. No significant unexpected AEs occurred. Seven pts have been withdrawn: five due to progressive disease, one due to performance status, and one due to prolonged myelosuppression (DLT). Four pts are ongoing: one with stable disease after 3 cy (at 480 mg/m^2/d).
Conclusions: MTD is not reached. No unexpected AEs have occurred. CP-4126 is well tolerated by pts with solid tumours up to 800 mg/m^2/d in a d1, 8, 15 q4w schedule. Accrual is ongoing. Updated results including PK will be presented.

726 POSTER

Antitumor activity and reversal of multidrug resistance by the newly synthesised oleanolic acid derivative – methyl-3,11-dioxoolean-12-en-28-oate

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The aim of this study was to compare the cytotoxic effect of the newly synthesised oleanolic acid-derivative methyl 3,11-dioxoolean-12-en-28-oate (BB.136) in tumor and normal cells with its parent compound oleanolic acid. We also investigated the ability of the compound to reverse multidrug resistance, inhibit P-gp activity, arrest the cell cycle and to induce apoptosis. We used 7 cancer cell lines (MCF7, MCF7/ADR, HL-60, HL-60/AR, CCRF-CEM and CCRF-VCR1000) and one normal cell line (MCF10A). The growth inhibitory activity of BB.136 was assessed using MTT and SRB assays. Cell cycle analysis and induction of apoptosis were determined with propidium iodide.
We observed stronger cytotoxic activity of BB.136 comparing to the control compound oleanolic acid. The antiproliferative efficiency of the tested compound was similar in MCF7 and its resistant subline MCF7/ADR. The IC_{50} values were 4.53 μM and 3.77 μM, respectively (oleanolic acid: 5.38 μM and 37.02 μM). A similar result was obtained in CCRF-CEM and multidrug resistant CCRF-VCR1000 cells. It suggests that MDR1 expressing cells are not resistant to the tested oleanolic acid derivative. The most sensitive of the tumor cell lines to BB.136 were CCRF-CEM and CCRF-VCR1000 (IC_{50} 1.69 μM and 1.56 μM, respectively). MCF10A cells were more resistant (IC_{50} 18.36 μM) to BB.136 than the cancer cells. Additionally the tested compound enhanced the activity of Adriamycin in CCRF-VCR1000 cells, indicating a reversal of resistance. Flow cytometer analysis showed that treatment of HL-60 cells with a 4-fold IC_{50} concentration of the tested compound for 48 hours induced apoptosis in 36.2% of cells.
BB.136 is more potent than the parent compound and is able to induce apoptosis in HL-60 cell. Its lower cytotoxic activity against normal cells and its multidrug resistance reversing ability indicates that it is an interesting compound for further development.

727 POSTER

PEGylation governs the disposition and metabolism of irinotecan following administration of a novel PEG–Irinotecan conjugate

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NKTR-102, a novel PEG-Irinotecan conjugate, is currently in Phase I clinical development. PEGylation dominated the disposition kinetics of NKTR-102 as demonstrated in rat studies where the plasma kinetics of NKTR-102 mimicked that of the 14C-PEG itself used in NKTR-102.
PEGylation of irinotecan enhanced the pharmacokinetic and pharmacodynamic behavior of the active metabolite SN38. Prolonged systemic SN38 exposure resulted in slow disposition and metabolism of NKTR-102. Intravenous administration of 260 mg/kg of 14C-PEG to rats resulted in distribution primarily within the circulatory system. The main route of excretion of the 14C-PEG was via urine where 61.1% of the administered radioactivity was recovered over ten days. Fecal excretion and other elimination routes accounted for 22.7% of the administered radioactivity over the same period.
Intravenous administration of either the 14C-PEG alone or NKTR-102 showed prolonged plasma exposure. At equivalent doses, the plasma clearances of the 14C-PEG alone or NKTR-102 were similarly small, 2.5 mL/hr·kg and 9−30 mL/hr·kg, respectively. In contrast, plasma clearance of irinotecan following irinotecan administration was 2320 mL/hr·kg, 100–300 times greater than that following NKTR-102 administration. Unlike NKTR-102, irinotecan distributed extensively in the tissue compartment and minimally in the plasma compartment.
In the rat, NKTR-102 volume of distribution was comparable to the vascular compartment volume, which contributed to the observed high plasma exposure of NKTR-102. These results, combined with a lower clearance of SN38 derived from NKTR-102, resulted in notably greater exposure to SN38.
In summary, the PEG component of NKTR-102 dominated its disposition kinetics, resulting in greater and sustained systemic exposure to irinotecan and SN38.

728 POSTER

Differential inhibitory effects of epigallocatechin-3-gallate (EGCG) and C75 in cancer fatty acid metabolism

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Background: Endogenous fatty acid metabolism is crucial to maintain the cancer cell malignant phenotype. Lipogenesis is regulated by the enzyme fatty acid synthase (FASN); and fatty acid oxidation pathway is regulated by carnitine palmitoyltransferase-1 (CPT-1). Inhibition of FASN has been shown to induce apoptosis in a variety of cancer cells, and consequently to be a potential therapeutic target for the treatment of cancer. To date, only a few inhibitors of FASN have been reported (cerulenin, C75, EGCG, orlistat, triclosan), although the degree of specificity of this inhibition has not been addressed.
Material and Methods: We have evaluated the effects of C75 and (−)-epigallocatechin-3-gallate (EGCG) on fatty acid metabolism pathways (FASN and CPT-1 activities), cellular proliferation, induction of apoptosis and cell signalling (HER2, ERK1/2 and AKT cascades) in breast cancer cells and the effect of reduced FASN activity on adipocyte differentiation of 3T3-L1 cells.
Results: C75 and EGCG had comparable effects in blocking FASN activity. Treating cancer cells with C75 or EGCG induced apoptosis and caused a decrease in the active forms of oncoprotein HER2, AKT and ERK1/2 to a similar degree. In addition, C75 and EGCG reduced dramatically visible lipid droplet accumulation during preadypocite differentiation. We observed, in contrast, marked differential effects between C75 and EGCG on fatty acid oxidation pathway. While EGCG had either no effect or a moderate reduction in CPT-1 activity, C75 stimulated CPT-1 activity (up to 129%), even in presence of inhibitory levels of malonyl-CoA, a potent inhibitor of the CPT-1 enzyme.
Conclusions: In cancer cells, pharmacological inhibition of FASN occurs uncoupled from the stimulation of CPT-1 with EGCG but not with C75, suggesting that EGCG might be free of the CPT-I related in vivo weight-loss that has been associated with C75. Our results establish EGCG as a potent and specific natural inhibitor of fatty acid synthesis (FASN), which may hold promise as a target-directed anticaner drug.

729 POSTER

Safety, maximum tolerated dose and pharmacokinetics of a novel micellar formulation of paclitaxel in the treatment of recurrent solid tumours – a phase I/II study

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Background: Paclitaxel (Taxol®) treatment requires extensive premedication, slow infusion (3−24 h) and a close monitoring mainly due to effects caused by the solvent castor oil (Cremophor EL®). Paclitaxel,

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.

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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