ever, the clinical response rates obtained remain modest. MEN4901/T-0128 is a polysaccharide conjugate prodrug composed by the camptothecin derivative T-2513 bound to a carboxymethyldextran moiety via a triglycine spacer, endowed with a remarkable antitumour activity in a large panel of human tumour models of different histotypes. The purpose of the present study is to evaluate, in vivo, the growth-inhibitory effects of MEN4901/T-0128 in comparison with CPT-11, in a panel of human gastrointestinal tumours, i.e. human pancreas (ASPC-1, Capan-1), colorectal (HCT-116), gastric (HGC-27, NCI-N87) and oesophageal (OE-21) carcinoma, xenografted s.c. in nude mice. The two compounds were administered i.v. at the previously established optimal schedule of 60 mg/Kg bi-weekly (q4dx4) for CPT-11, and 80 or 160 mg/Kg as a single dose for MEN4901/T-0128. In all xenografted carcinomas MEN4901/T-0128 exerted a remarkable and significant antitumour activity, always superior to CPT-11, in terms of both tumour volume inhibition (TVI%) and log cell kill (LCK). In particular, MEN4901/T-0128 drastically reduced the growth of tumours fully resistant to CPT-11, like the gastric NCI-N87 (TVI= 98%, LCK=2.3), the pancreas ASPC-1 (TVI=88%, LCK=1.9) and Capan-1 (TVI= 99%, LCK >5), and the oesophageal OE-21 carcinoma (TVI=96%, LCK=1.6). Interestingly, against pancreatic carcinoma Capan-1, the efficacy of MEN4901/T-0128 resulted in a prolonged tumour growth inhibition; the tumours remained undetectable up to 100 days. In conclusion, a single administration of MEN4901/T0128 was active against all the gastrointestinal models evaluated, including naturally CPT-11 resistant tumours. These data further confirm the superior efficacy and the broader spectrum of antitumour activity of MEN 4901/T0128 in comparison with CPT-11.

551 POSTER

Peripheral Blood CD3(+) T cells, independent on their cell-cycle status, are inherently resistant to high concentrations of arsenic trioxide

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Arsenic trioxide (ATO) has been successfully used to treat acute promyelocytic leukemia (APL). The potential of ATO in other cancers are currently under investigation. It is critical to understand the toxicity of ATO to normal peripheral blood cells (PBC). Previously, we have previously demonstrated that ATO sensitivity to leukemic cells was related to cell- cycle status. In this study, we examined the toxicity of ATO in different subsets of PBC. PBC were treated with 0, 0.1, 1, 2, and 5 microM of ATO for 3 and 7 days before phenotypic analysis by flow cytometry. We chose CD15 and CD33 for myeloid cells, CD19 for B cells and CD3 for T cells. Our results showed that the toxicity of ATO to normal PBC, like to leukemic cells, was time- and dose-dependent. We found that ATO toxicity to PBC was not evident at low concentrations (< 1 microM). At high concentration, only CD3+ T cells (95.8%) could survive. Further analysis of the expression of CD4 and CD8 on these ATO-resistant CD3+ cells showed that CD3(+)CD4(+) cells were relatively resistant to ATO compared with CD3(+)CD8(+) cells (62.2% vs 30.5%). But, proliferation kinetics between different subsets of PBC did not differ when estimated by cell-proliferation analysis using CFSE This indicated that the cell cycling did not play a major role in the ATO resistance found in CD3(+) T cells. The expression of MDR1 was not related to the ATO resistance in CD3(+) T cells, when measured by rhodamine-123 efflux. We also found that cells that underwent apoptosis had altered mitochondrial transmembrane potential estimated by differential staining of rhodamine-123 when rhodamine-123 efflux was blocked by MDR1 inhibitor, verapamil, indicating that ATO- mediated apoptosis was most likely mediated by intrinsic mitochondrial pathway. Our results suggested that there could be multiple mechanisms responsible for the sensitivity to ATO, which might play a role in the toxicity observed during the clinical use of ATO. Identification of the mechanisms responsible for these two different types of cells could be useful to ATO- containing regimens for cancers other APL.

552 POSTER

Evaluation of the pharmacokinetic (PK) interactions between cetuximab and irinotecan in patients with Epidermal Growth Factor Receptor (EGFR)-expressing advanced solid tumors. Results of a phase I study.

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Background: Cetuximab (Erbitux™) is a chimeric monoclonal antibody, which has shown activity in patients with EGFR-expressing metastatic colorectal cancer (CRC) refractory to prior chemotherapy with irinotecan.

Objectives: This study investigated the impact of cetuximab on PK parameters of irinotecan, and that of irinotecan on PK values of cetuximab in patients with a variety of tumor types.

Methods: Group A received irinotecan from week 1 (350 mg/m^2 q3wks), with cetuximab added in week 2 (400 mg/m^2 1st infusion, then 250 mg/m^2 weekly). Group B received cetuximab weeks 1 to 4 (400 mg/m^2 1st infusion, then 250 mg/m^2 weekly), with irinotecan added in week 4. Patients were treated until progression or impaired tolerance.

Results: 15 patients were enrolled and 13 were evaluable for PK. Patient demographics for group A were median age=56 years and KPS=80, and a 3/3 male/female gender split. The group B demographics were median age=49 years and KPS=80, and a 3/4 male/female ratio. With the exception of a prostate cancer patient in group B, all patients had tumors of gastrointestinal origin. The median treatment duration was 10 weeks. Drug-related adverse events were consistent with the safety profiles of the drugs and consisted of grade 2 fever in two patients in close temporal relationship with the administration of cetuximab and grade 3 diarrhea in two patients in week 4 after irinotecan administration. Minor responses and tumor stabilizations were reported. Concentration-time profiles of cetuximab, when given alone or in combination with irinotecan, were superimposable. The same was true for irinotecan. Derived PK parameters for cetuximab and irinotecan were similar after mono- and combined administration (Table). The calculated ratios for all the irinotecan PK parameters at week 4 over week 1 ranged from 90-112% (group A), showing that the presence of cetuximab did not impact on the single-dose PK of irinotecan. The calculated ratios for all the cetuximab PK parameters at week 4 over week 3 ranged from 87-123% (group B), showing that the presence of irinotecan did not impact on the PK of cetuximab.

Gp	Pts	Treatment	Week	Analyte	AUC_{0-t} (μg/mL*h)	C_{max} (μg/mL)	t_{max} (h)	$t_{1/2}$ (h)
A	6	Irinotecan alone	1	Irinotecan	42.8	8.13	1	10
		Irinotecan+cetuximab	4	Irinotecan	39.1	6.78	1	10
B	7	Cetuximab alone	3	Cetuximab	13039	153	2	119
		Cetuximab+irinotecan	4	Cetuximab	14923	162	2	117

Mean values listed

Conclusion: Results of this study indicate the absence of any appreciable PK interaction between the two compounds.

553 POSTER

Alternate administration sequences of gemcitabine / vinorelbine in advanced solid tumor: a pharmacokinetic study.

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The aim of this study was to investigate a possible pharmacokinetic (PK) interaction between gemcitabina (GEM) and vinorelbine (VNR), when co-administered following the alternate sequence GEM-VNR and VNR-GEM. GEM-VNR sequence: 9 patients with advanced NSCLC or metastatic breast cancer were treated with GEM (60'iv, 1000mg/m^2) followed after 5' by VNR (10'iv, 25mg/m^2) on day 1 and 8 every 3 weeks; VNR-GEM sequence:17 patients received VNR followed by GEM at the same doses and regimen; 5 patients were given only single-agent GEM (60'iv, 1000mg/m^2) as a control group (GEM group). GEM PK profile in both schedules showed biphasic elimination as in monotherapy GEM group; GEM C and AUC values are higher in the GEM group than in GEM-VNR and VNR-GEM sequences (31.62mg/l vs 23.41mg/l and 28.74mg/l for C and 28.17mg*h/l vs 19.37mg*h/l and 23.76mg*h/l for AUC) . GEM Ke and Vss were significantly