1115 POSTER*

Phase I and pharmacokinetic study of CHOP/MGBG (CM) in patients with Non-Hodgkin's-Lymphoma

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Purpose: To determine the Maximum Tolerated Dose (MTD), Dose Limiting Toxicity (DLT) and pharmacokinetics of M when combined with C.

Methods: Phase I study with increasing doses of M (400–700 mg/m^2) q 21 days in patients (pts) with intermediate or high-grade Non Hodgkin's-Lymphoma.

Results: 28 pts are evaluable for toxicity (t) (CTC), 22 for response (r) (WHO) and response duration (rd):

Dose MGBG	No of pts t/r	WBC 3/4	ANC 3/4	CR	PR	rd/range (months)
400 mg/m^2	13/12	5/6	0/11	5	5	17+/3+–26+
500 mg/m^2	6/4	2/4	0/6	3	1	12+/9+–14+
600 mg/m^2	6/4	2/4	0/6	2	2	8.5+/6+–9+
700 mg/m^2	3/2	1/1	1/2	0	2	4+/1+–7+

Thrombocytopenia grade 3 occurred in 1 pt at 400 mg/m^2, non-hematologic t grade 3/4 consisted of infection grade 3 in 1 pt at 400 mg/m^2. 6 pts were evaluated with 18 FDG-positron emission tomography at days 0, 8 and 42. Median decrease of 18 FDG-uptake on day 8 was 75% (range 56–86%) and on day 42 85.7% (range 85.7–88.5). Pharmacokinetic parameters at 400 mg/m^2 were: $t_{1/2\alpha}$ 0.19 h, $t_{1/2\beta}$ 2.07 h, $t_{1/2\gamma}$ 135.91 h, AUC 88.76 μgxh/mL, CL 5.19 L/h/m^2. Accrual is ongoing to determine the MTD of CM.

Conclusion: M can be combined with C at full doses. CM is a safe and active regimen warranting further evaluation.

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1116 POSTER*

A phase I study of MTA (multi-targeted antifolate, LY231514) plus cisplatin (CIS) in patients with advanced solid tumours

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Purpose: MTA (LY231514) is a novel multi-targeted antifolate that inhibits thymidylate synthase and other folate-dependent enzymes. It has shown antitumour activity in preclinical models and early clinical trials. The study objectives were to determine the maximum tolerated dose (MTD) and dose-limiting toxicity of MTA (as a 10-min infusion) followed by CIS (1-hr infusion), every 21 days.

Methods: Pts with advanced/metastatic solid tumours (WHO PS ≤ 2) for whom no better treatment was available were eligible. Five dose levels were evaluated.

Dose level (mg/m^2)		Number of:		CTC Grade III/IV toxicity (# pts)		
MTA	CIS	pts	courses	neutropenia	leucopenia	↓platelets
1) 300	60	6	23	0/1	2/0	0/1
2) 300	75	6	16	5/1	4/0	0/0
3) 400	75	6	13	2/1	1/0	0/0
4) 500	75	3	5	0/5	0/0	0/2
5) 600	75	5	ongoing	0/0	0/0	0/1

Results: To date, 26 pts have been enrolled (4 F/22 M; median age 57 years, range 43–73). One pt developed Grade III mucositis. No major liver or renal toxicity was observed. The MTD has not yet been reached. Partial responses were noted at Level 1 (1 NSCLC; 1 colorectal), Level 2 (1 gastric) and Level 3 (1 unknown primary).

Conclusions: MTA and CIS can be given together at full doses. This combination shows promising activity in patients with advanced/metastatic solid tumours.

1117 POSTER*

Phase I study of Interleukin-4 (rHuIL-4) combined with chemotherapy in gastrointestinal (GI) malignancies

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IL-4 is a pleotropic cytokine which has shown tumor growth inhibition and synergy with chemotherapy in animal models. The safety of rHuIL-4, given in combination with 5-FU/Leucovorin (FA) chemotherapy, was evaluated in 15 patients (pts) with advanced GI malignancies. Cohorts of 3–6 pts received rHuIL-4 by SC injection, TIW for 4 weeks at dose levels of 0.5, 2.4 or 8 μg/kg, as well as 5-FU (425 mg/m^2) plus FA (25 mg/m^2) by daily IV infusion for 5 days in Wk1. In addition to standard safety evaluations, measurement of the kinetic (PK) profile of 5-FU was performed on D1 and D4. Age range was 26–74; 9 were male and 14 had colorectal tumors. Six pts had prior radiation; 10 had prior FU-based chemotherapy. The most frequently reported adverse experiences in the study were fatigue, nausea and fever (67–87%), which are expected from the known safety profiles of FU, FA or rHuIL-4. Grade 4 toxicities included neutropenia, headache, mucositis and vomiting (13–20%). No new toxicities were reported that were related to the combination of agents. DLT was seen in ≤2 pts in each cohort and an MTD for rHuIL-4 was not reached. PK analysis showed that concommitant administration of rising multiple doses of rHuIL-4 did not appear to effect the kinetics of 5-FU. Based on overall tolerability, a dose of 4.0 μg/kg rHuIL-4 was selected for further evaluation. Additional chemotherapy combinations will also be explored.

1118 POSTER

Absolute bioavailability and pharmacokinetics (PK) of oral vinorelbine (VRL) in patients (pts) with solid tumors

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The aim of this study was to compare body exposure and acute side effects of VRL administered either as an IV infusion (25 mg/m^2) or as capsules (80 mg/m^2), a new formulation. This was an open randomized Phase I-PK with cross-over design (one-week wash-out period). 25 and 31 pts out of 32 included are evaluable for PK and safety analysis respectively. Safety results: hematological toxicity: no significant difference between oral and IV VRL (G3–4 neutropenia: PO 27% – IV 10%). Nausea, vomiting: significant difference is observed when all grades are pooled (PO > IV) but grades 3–4 are rare and not different (G3 nausea: PO 3.3.% – IV 0%; G3–4 vomiting: PO 6.6% – IV 6.7%). Assuming dose-proportionality in both routes, bioavailability of the oral form is 43% ± 14. Higher blood AUCs are observed after oral administration as compared to IV ($p < 0.05$). Moreover, no increase in inter-individual variability is demonstrated for oral route compared to IV.

1119 POSTER

Phase I clinical study of ecteinascidin-743 (ET-743) as a 24 hours continuous intravenous infusion (CI) in patients (pts) with solid tumors (st): A progress report

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ET-743 is a tetrahydroisoquinolone alkaloid from the tunicate *Ecteinascidia turbinata*, potently active in a variety of *in vivo* human xenograft models with long lasting complete remissions in melanoma, non small cell lung, breast and ovarian carcinoma. This activity may result from its unique mechanism of action as a DNA minor groove binding agent (guanine N2-specific sequence selectivity). Target organs in preclinical toxicity were bone marrow and liver. Pts with histological diagnosis of advanced stage ST, ECOG ≤ 2 and normal bone marrow, liver, renal function receive ET-743 iv 24 h CI every 21 days. As of 11/2/97, 11 pts were entered. Median age = 54 y (28–67) women/men = 7/2, median ECOG = 1 (0–2). Tumor types included breast (1), bladder (1), larynx (1), ovary (2), rectum (1), renal (3), gastric (1), and ACUP (1), all refractory to standard chemotherapy. Pharmacokinetics are performed on day 1 and day 2, and NCI-CTC grading criteria are applied for toxicity.

The 11 pts received 31 cycles (cy) with a median number of cy/pt = 2 (1–8). Current data by dose level are listed below.

Dose level ($\mu g/m^2$)	N° pts	N° cycles	Comments
50	3	5	–
100	3	16	1 pt g1 emesis
200	3	8	1 pt g1 emesis
400	2	2	–

No toxicity except 2 episodes of grade 1 emesis has been observed. Dose escalation continues, currently nearing the expected pharmacoactive range level. Simultaneous PK evaluation is ongoing.

1120 POSTER

A phase I trial of gemcitabine plus paclitaxel combination therapy in patients with refractory solid tumors

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Paclitaxel (P) and gemcitabine (G) have exhibited activity as single agents in a variety of malignancies. Recently, P has been shown to have unique activity when dosed on a weekly basis. We then developed a dose escalating phase I study combining P and G with each administered once weekly for 3 weeks out of 4. The starting dose for P was 60 mg/m2 intravenously (IV) over 3 hours (hr) and for G 600 mg/m2 IV over 30 minutes, administered after the P dose. Patients (pts) were premedicated for P with dexamethasone, diphenhydramine and cimetidine in the usual fashion. All patients must have histologic evidence of a refractory solid tumor and have received no more than one prior chemotherapy regimen. Pts must not have received prior P or G. All patients must have adequate renal and hepatic function. To date, 10 pts have been entered on study. Eight pts are fully evaluable for response and toxicity. Five pts were treated on level one with one patient experiencing a dose-limiting toxicity (DLT) with >5 days of grade 4 neutropenia without fever. One pt on dose level 2 experienced grade 3 dyspnea. There have been no neutropenic fevers. There have been two documented responses, a patient with esophageal cancer, previously treated with Mitomycin, Ifosfamide and Cisplatin and a patient with previously untreated carcinoma of unknown origin. This study continues to accrue patients.

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1121 POSTER

Pharmacokinetics of Irinotecan (CPT-11) and 5-fluorouracil (5-FU) in a dose finding study in adult patients with solid tumours

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Purpose: To define kinetic parameters of CPT-11 and its active metabolite (SN38) after a 90 min. infusion when associated with a continuous infusion of 5-FU (250 mg/m²/day) for 14 days in patients with solid tumours.

Methods: To date drug kinetics have been determined in 10 patients receiving CPT-11 in a dose escalation scheme with total doses of 150 (n = 3), 175 (n = 3), 200 (n = 2), 250 (n = 2) mg/m². Plasma concentrations of CPT-11 and SN38 were determined as total lactone form and 5-FU levels were measured by HPLC over a 0–168 h period. Pharmacokinetic parameters were calculated using siphar programme and are summarized in the following table.

Results: mean (± SD) – AUC (mcg/L/h), Cmax (mcg/L), tl/2 (h), Cl (L/h/m²)

	AUC/Dose	Cmax/Dose	t1/2	C1
CPT11	98.3 (20.4)	19.2 (3.6)	11 (3)	11 (3)
SN38	1.3 (0.8)	0.3 (0.1)	5.7 (6.1)	–

The determination of 5-FU plasma concentrations is on-going.

Conclusions: These preliminary data suggest linear kinetics of CPT-11 related to dose. As previously reported, SN38 AUC is about 100-fold lower than CPT-11. Compared to single agent data, The co-administration of 5-FU does not seem to influence the PK of CPT-11.

1122 POSTER

Clinical and pharmacokinetic phase I study with Cematodin® given as continuous 24-hour intravenous infusion

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Purpose: To study the toxicity and anti-cancer effects of a new anti-cancer agent (LU103793, Cematodin), which is a pentapeptide interfering with the tubulin system.

Method: Thirty advanced cancer patients were enrolled into this study. The drug dose started at 10 mg/m² and was escalated to 27.5 mg/m². The drug was given as 24-hour infusion in 3-week intervals.

Results: The dose limiting toxicities were: myelotoxicity, hypertension and asthenis. No partial/complete response was observed, but minor regression and no change were seen. The c(t)-curves were best described by a two-compartment model. The pharmacokinetics is linear. Up to a maximum of about 50% was excreted into the urine.

Conclusions: The dose recommendation for phase II studies is 20 mg/m². A close patient monitoring during therapy is suggested.

1123 POSTER

Is Chatelut formula applicable in obese patients for predicting carboplatin clearance?

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Purpose: We previously proposed a formula to predict carboplatin clearance (CL) from four patient characteristics: plasma creatinine level, body weight (wt), age, and sex [J Natl Cancer Inst 87: 573, 1995]. Its accuracy was studied in a subpopulation of obese patients (pts).

Methods: 25 pts (16 male and 9 female, 23 to 82 years old) were studied. Their overweight ranged from 20 to 67% (median 36%) of the ideal body weight calculated according to the Lorentz equation. Their actual CL were obtained individually by Siphar program. The pharmacokinetic population program Nonmem was used to determine the best value of substitution for wt in the formula.

Results: By using the actual wt, CL were significantly overpredicted (by more than 20% for 7/25 pts). By using the mean value between the ideal and the actual wt, a good prediction of CL was obtained: the percent error ranged from −33 to 39% and was comprised between −22 and 22% for 23/25 pts.

Conclusion: The formula is applicable to obese patients only if both ideal and actual weights were taken in account.

1124 POSTER

Optimizing the efficacy of epirubicin as an intravesical chemotherapy agent. Can it be buffered to ph 8?

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Purpose: The use of epirubicin in the treatment of bladder cancer is well established, however there is scope for improvement in the responses obtained. Such weak bases should be taken up more readily by cells at higher pH, but the evidence that this translates into increased toxicity or that the drug would not degrade is yet unpublished.

Methods: a) Three variants of the MGHU-1 bladder cancer cell line were pulsed with serial dilutions of buffered for 2 hours in 96-well plates. The MTT assay was used to assess cytotoxicity 5 days later. Drug uptake was assessed by flow cytometry and confocal microscopy. b) Thin layer chroatography was performed on drug held at various pH levels for times up to 48 hours.

Results: There was a near linear increase in the uptake of epirubicin between pH6 and pH8. High pH increased cytotoxicity and improved the efficacy of drug resistance reversing agents. Negligible breakdown of drug occurred in 2 hours, some degradation was evident at 24 hours at pH $\geq$ 7.5

Conclusion: Intravesical epirubicin might well be more effective if buffered to a mildly alkaline pH directly before instillation.