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A PHASE I STUDY OF THE ANTINEOVASCULARIZATION DRUG CM-101. R. DeVore, C. Hellerqvist, G. Wakefield, B. Wamil, G. Thurman, H. Sundell, R. Jotte, H. Yan, C. Carter, Y-F Wang, G. York, M. Zhang, and D. Johnson. Vanderbilt University, Nashville, TN 37232.

CM-101 is a bacterial polysaccharide that induces neovascular inflammation in malignant tumors. Twenty seven patients with refractory malignancies were enrolled in a phase I study of CM-101. The first 15 patients (Group 1) received CM-101 intravenously by a 15-minute infusion every other day, three times in one week, at doses ranging from 1 unit (7.5μg)/Kg to 5 units/Kg. Cycles were repeated every 3-4 weeks. Twelve additional patients (Group 2) were treated on a weekly x 10 schedule, of which six received 3.3 units/Kg and 6 received 2 units/Kg of CM-101. Serum was analyzed for the development of CM-101 IgG and IgM. Inflammatory cytokines were analyzed following each treatment. For the Group 1 patients the maximally tolerated dose was 3.3 units/Kg and dose limiting toxicities included grade IV dyspnea and arrhythmia encountered at the 5 units/Kg level. Toxicities occurred primarily within the first 12 hours following therapy and included mild to moderate fever/chills, nausea, cough, headache, facial flushing, dyspnea, myalgias, and acute tumor-related pain. No patient developed detectable CM-101 antibodies. All patients experienced marked time- and dose-dependent elevations in all cytokines studied. Peak cytokine ranges (pg/ml) were as follows: TNFα (243 - 4,922); mip-1α (535 - 8,174); IL-6 (212 - 10,150); IL-8 (1,582 - 16,155); IL-10 (80 - 1,463); sE-selectin (149 - 1,259 ng/ml). In both patient groups peak TNFα and IL-8 responses occurred following the first treatment, but were attenuated following the 2nd and 3rd treatments. However, when Group 1 patients received subsequent treatment cycles following a 2-3 week rest, peak cytokine levels were similar to those observed following their initial treatment. This may indicate that a more treatment interval is necessary to generate the desired repetitive inflammatory response. CM-101 can be safely administered at doses that produce evidence for severe, and possibly tumor specific, inflammation. Supported by CarboMed, Inc. and GCRC, MO1 RR00095.

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A PHASE I EVALUATION OF LY231514, A NOVEL MULTI-TARGETED ANTIFOLATE, ADMINISTERED EVERY 21 DAYS. DA Rinaldi, HA Burris, FA Dorr, G Rodriguez, SG Eckhardt, SM Fields, JR Woodworth, JG Kuhn, C Langley, G Clark, P Lu, DD Von Hoff. From the Cancer Therapy and Research Center and Brooke Army Medical Center, San Antonio, TX, and Eli Lilly and Company, Indianapolis, IN.

LY231514 (N-[4-[2-(2-amino-4,7-dihydro-4-oxo-1H-pyrrolo,3-d] pyrimidin -5-yl) ethyl] benzoyl]-L-glutamic acid disodium salt) is a multi-targeted antifolate compound which inhibits the enzymes thymidylate synthase and dihydrofolate reductase. Escalating doses were administered intravenously every 21 days to patients with advanced, refractory, solid tumors to assess toxicities and determine the maximally-tolerated dose (MTD), pharmacokinetic profile, and potential antitumor activity of the compound. Dose escalation was based on the Modified Continual Reassessment Method, with 1 patient treated at each minimally toxic dose level. A total of 37 patients (27 males, 10 females, median age 59 yo, median PS 90%) were treated with 132 courses at 9 dose levels, ranging from 50 to 700 mg/m^2. The MTD of LY231514 was 600 mg/m^2, with reversible neutropenia, thrombocytopenia, and fatigue as the dose-limiting toxicities. Nonhematologic toxicities observed included mild to moderate fatigue, anorexia, nausea, diarrhea, mucositis, rash, and reversible hepatic transaminase elevations. Pharmacokinetic analysis after the first course of treatment at the 600 mg/m^2 dose level demonstrated a mean harmonic half-life, maximum plasma concentration, clearance, area under the curve (AUC), and apparent volume of distribution at steady-state of 5.07 hours, 142 mcg/ml, 41.7 ml/min/m^2, 293.3 mcg-hr/ml., and 26.55 L/m^2 respectively. Seventy-eight percent of the compound was excreted unchanged in the urine. Partial responses were achieved in 2 patients with advanced pancreatic cancer and in 2 patients with advanced colorectal cancer. Minor responses were obtained in 6 patients with advanced colorectal cancer. LY231514 is a promising agent for the treatment of gastrointestinal malignancies.

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A PHASE I TRIAL TO EVALUATE ORALLY ADMINISTERED IRINOTECAN HCL (CPT-11) GIVEN DAILY X 5 EVERY 3 WEEKS IN PATIENTS WITH REFRACTORY MALIGNANCIES. R. Drengler, H. Burris, A. Dietz, J. Eckardt, G. Eckhardt, S. Hodges, M. Kraynak, J. Kuhn, N. Peacock, D. Rinaldi, J. Rizzo, G. Rodriguez, L. Schaaf, L. Smith, A. Thurman, D. Von Hoff. The University of Texas Health Science Center, San Antonio, TX, Cancer Therapy & Research Center, San Antonio, TX, Brooke Army Medical Center, Ft Sam Houston, TX, and The Upjohn Company, Kalamazoo, MI.

Irinotecan (CPT-11), a semi-synthetic water soluble camptothecin derivative, is a topoisomerase I inhibitor with substantial antitumor activity. It has been studied clinically in a variety of dosing schedules by the intravenous route. The development of an oral formulation would provide the opportunity for cost-effective outpatient therapy, enhance quality of life by preventing prolonged stays at cancer clinics for intravenous infusions and allow for convenient administration of chronic dosing regimens. The objectives of this study were to determine the maximally-tolerated dose (MTD) and the dose limiting toxicity of irinotecan when administered orally, once a day for five consecutive days; to characterize the pharmacokinetics of irinotecan and its metabolite, SN-38; and to detect any evidence of antitumor activity. To date, 13 patients (pts) (8 male, 5 female, ages 29-74) with advanced refractory solid tumors have received 40 courses of treatment over 4 dose levels (20, 40, 66 and 100 mg/m^2/day) on a daily x 5 every 3 weeks schedule. The majority of patients treated had 5-FU refractory metastatic colon cancer (12/13). Entry criteria included good organ function, performance status 0-2, adequate hematologic status and absence of any condition which could impair oral medication intake. Irinotecan was administered diluted in 50 ml of Cran-Grape® juice. Patients fasted 4 hrs prior and 2 hrs post oral administration. Dose limiting toxicities included diarrhea and neutropenia. Grade 4 diarrhea (despite use of aggressive loperamide support) occurred in 1/1 pt at 100 mg/m^2/d and 2/6 pts at 66 mg/m^2/d. Grade 4 neutropenia occurred in 1/1 pt at 100 mg/m^2/d and 1/6 pts at 66 mg/m^2/d. Further patient accrual to better define the dose recommended for phase II studies is currently in progress. All other toxicities were grade 2 or less. Pharmacokinetic analysis including concentrations of lactone, total and glucuronide forms of irinotecan and its metabolite SN-38 quantified by high performance liquid chromatography is ongoing. Supported by the Upjohn Company.

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EVERY OTHER WEEK IRINOTECAN (CPT-11): RESULTS OF A PHASE I AND PHARMACOKINETIC (PK) STUDY. M.L. Rothenberg, D.A. Rinaldi, L.S. Smith, L.J. Schaaf, S. Hodges, A.M. Thurman, N.K. Ichhpurani, S.G. Eckhardt, G.I. Rodriguez, M. Villalona, R. Drengler, A.J. Dietz, T.C. Murphy, H.A. Burris, III, D.D. Von Hoff. The University of Texas Health Science Center at San Antonio, TX. Cancer Therapy and Research Center, San Antonio, TX, Brooke Army Medical Center, Ft. Sam Houston, TX and The Upjohn Co., Kalamazoo, MI.

Irinotecan hydrochloride (CPT-11) is a water-soluble camptothecin analog with promising activity against colorectal, small cell and non-small cell lung, ovarian, and cervical cancers. While a once every 3 week (wk) schedule allows administration of higher single doses and results in a slightly higher dose intensity, weekly drug administration allows for more frequent dosing, which may be important for a cell-cycle specific drug such as this. It is possible that an every other wk drug administration schedule could combine the most favorable aspects of dose intensity and dose frequency. We are conducting a Phase I and PK trial of this drug administration schedule. To date, 20 patients (pts) have been enrolled (13 M 7 F) and all are evaluable for toxicity during cycle 1. Median age: 53.5 (range: 29-77). WHO PS 0:13, 1:6, 2:1. Thirteen pts have colon cancer, 5 rectal cancer, 1 adenoca of the small bowel, and 1 adenoca of unknown primary. Clinical toxicities are as follows:

Dose Level (mg/m^2)	# Pts Evaluable/ Entered	# Cycles Administered	Median ANC Nadir Cycle 1 (cells/mm^3) (range)	# Pts With DLT (Type of DLT)
125	4/4	22	2825 (1417-5548)	0
150	3/3	31	1699 (347-3574)	0
175	6/6	46	2831 (160-4935)	1 (Febrile neut. and grade 4 ANC x 5 days)
200	6/6	32	2672 (300-3637)	1 (Febrile neut. and grade 4 diarrhea)
225	1/1	1	4500	0

Other common toxicities have been nausea, vomiting, fatigue, and anorexia, none of which have been dose limiting. Preliminary PK data from the first 3 dose levels reveal a linear relationship between drug dose, $C_t$max and AUC for CPT-11, but not for SN-38. Pharmacodynamic relationships will be evaluated once MTD is reached. One pt with colon cancer has had a confirmed PR and 3 others have had a fall in CEA of $\geq$ 50%. With an MTD $\geq$ 200 mg/m^2, this schedule has a dose intensity that will approach or exceed the q 3 wk schedule ($\geq$ 100 mg/m^2/wk vs. 116.7 mg/m^2/wk, respectively) while administering drug 33% more frequently. Accrual to the 225 mg/m^2 dose level is ongoing. In conclusion, every other wk administration of CPT-11 is feasible and may provide the optimal balance between dose intensity and dose frequency. This study was sponsored by The Upjohn Company.