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A PHASE I AND BIOAVAILABILITY STUDY OF ORAL TOPOTECAN

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Topotecan (T) is an inhibitor of topoisomerase I undergoing clinical development. The oral bioavailability (F) of T in dogs is 36%, however, bioequivalent toxicity is closer to 100%. The objectives of this study were to determine the MTD (part 1) and absolute F (part 2) of T. All patients (pts) fasted 4 hours prior to and 2 hours after treatment with oral T. Pharmacokinetic analysis was performed by HPLC. In part 1, 12 pts (median age 63, median PS 1, 6 M/6 F) received a total of 51 courses of therapy. The initial starting dose of 17.5 mg/m^2 was well tolerated IV but was accompanied by grade 4 neutropenia and thrombocytopenia when given orally. The oral dose was reduced to 14.0 mg/m^2 where 1/6 patients developed grade 4 neutropenia. Non-hematologic toxicities were mild (<grade 2). In part 2, 18 pts were randomized to either 14.0 mg/m^2 oral T on cycle 1 and 17.5 mg/m^2 IV on cycle 2 or visa versa. T demonstrated 44% F with rapid oral absorption (peak 0.74 hr) and peak lactone conc. (50 ± 22) 10× less than IV (493 ± 221 ng/ml). There was no difference in clearance or Vdss. The AUC achieved PO (275 ± 113) is 2.8× lower than IV (776 ± 167 ngxhr/ml). APR in a pt with H&N cancer and a MR in a pt with melanoma were observed. Even with lower peak conc and AUC's, oral T maintains it's biologic activity.

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PHASE I TRIAL OF THE TOPOISOMERASE I INHIBITOR GG211 AS A 72-HOUR INFUSION

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In a Phase I trial of the water soluble camptothecin analog GG211, 44 patients received a 72-hour infusion at doses ranging from 0.25 to 2.5 mg/m^2/day. Myelosuppression is dose limiting. At doses ≥2.0 mg/m^2/day, 6 of 14 patients experienced grade 4 granulocytopenia and 2 of 14 grade 4 thrombocytopenia. Additional side effects (≥grade 2) included nausea, vomiting, anorexia, diarrhea, fatigue, and phlebitis. One patient at the highest dose had grade 3 mucositis in association with myelosuppression. Partial responses have been observed in ovarian, colon, and breast cancers and hepatoma. Additional minor responses have been observed in colon cancer. Whole blood GG211 lactone C_{ss} concentrations increased linearly with dose. The mean terminal half life was 7.5 ± 3.5 hrs, and mean clearance 922 ± 292 ml/min/m^2. Pharmacodynamic analyses demonstrated that steady-state concentrations were predictive of toxicity. Phase II studies with this novel compound are in progress.

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CLINICAL PHASE I TRIAL OF PK1 (HPMA CO-POLYMER DOXORUBICIN)

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PK1 is a novel compound consisting of N-(2-Hydroxypropyl) methacrylamide (HPMA) hompolymer bound to doxorubicin (DOX) via a peptidyl spacer which is cleaved intracellularly by lysosomal proteinases, (once the compound has entered the cell via endocytosis), releasing free DOX intratumourally. Improved antitumour activity compared to free drug has been demonstrated preclinically, especially in solid tumour models. The stability of the linkage in the bloodstream also reduces general toxicities such as cardiotoxicity and myelosuppression in animal studies, and we have therefore initiated a phase I clinical trial. The starting dose in humans was 20 mg/m^2 given as an i.v. infusion every 3 weeks. Concurrent pharmacokinetic studies and tumour imaging using radiolabelled drug are also being performed. To date 19 patients have been treated (ages 34–72, mean 57 years). Tumour types are: colorectal 3, ACUP 3, biliary tract 3, head and neck 2, NSCLC 2, breast 2, others 4. Dose levels 20 mg/m^2, 40 mg/m^2 and 80 mg/m^2 demonstrated CTC grade I nausea, vomiting and anorexia—toxicities also seen at higher dose levels. 3 patients were entered at 120 mg/m^2; grade I neurotoxicity (paraesthesia) (2/3), grade I hepatotoxicity (reversible transaminase elevations) (2/3) and grade I lethargy (1/3) was observed. Six patients have been entered at 180 mg/m^2. The first developed reversible grade III neurocerebellar toxicity. Other toxicities seen; grade II neutropenia (1/6), grade I mucositis (1/6) and grade II nausea (1/6) requiring prophylactic antiemetics. No alopecia or cardiotoxicity has been observed. One patient has been entered at 240 mg/m^2 (3–4× the MTD of free DOX) and has experienced grade II anaemia, and grade I emesis to date. There is evidence of antitumour activity, and the study continues to accrue patients.

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A CLINICAL PHASE I STUDY OF AN ANTI-CD25-DEGLYCOSYLATED RICIN A-CHAIN IMMUNOTOXIN (RFT5-SMPT-DGA) IN PATIENTS WITH REFRACTORY HODGKIN'S DISEASE

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Twelve patients with resistent Hodgkin's lymphoma were treated in an ongoing Phase-I trial with the immunotoxin (IT) RFT5-SMPT-dgA consisting of a moab directed against the α-chain of the IL-2 receptor (CD25) chemically linked to deglycosylated ricin A-chain. Selective toxicity of RFT5-SMPT-dgA has been demonstrated against Hodgkin/Reed-Sternberg cells *in vitro* and against solid and disseminated human Hodgkin's lymphoma in nude and SCID mice. All patients were heavily pretreated with a mean of 4 (range 2–7) different prior therapies including ABMT in 8 of 12. The mean age was 29 years (19 to 34). 11/12 patients had advanced disease (stage IV) with massive tumor burdens and 7/12 had B-symptoms. The IT was administered intravenously over 4 hours every other day for 7 days. Patients received one to four courses of 5, 10 or 15 mg/m^2. Peak serum concentration of intact IT as measured by ELISA was dose-related ranged from 7–780 pg/ml and T1/2s ranging from 1.5–9.7 hours (mean 4.8). Side effects were related to the vascular leak syndrome, i.e. decrease in serum albumin, edema, weight gain, hypotension, tachycardia, myalgia and weakness. In 2 patients an allergic reaction WHO grade 2 with generalized urticaria and mild bronchospasm occurred. At 15 mg/m^2 dosage 1 patient experienced grade 3 myalgia and 1 patient grade 2 thrombocytopenia. 7 patients made human anti ricin antibodies (>1 μg/ml) and none made human anti mouse antibodies (>1 μg/ml). 6 of 12 evaluable patients had progressive disease and 5 patients had stable disease and 1 patient a partial remission. The maximal tolerated dose has not been reached yet and enrollment continues.

931 POSTER

ORAL FOLIC ACID IMPROVES LOMETREXOL TOXICITY PROFILE: A PHASE I STUDY

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Lometrexol, the antipurine antifolate, has an MTD of 12 mg/m^2 when given as a single agent every 4 weeks. The dose limiting toxicities, myelosuppression and diarrhea, were substantially reduced in mice given a high folic acid diet. In an ongoing phase I dose escalation study of lometrexol coadministered with folic acid (5 mg/day for 14 days), 32 patients received lometrexol at doses of 12 mg/m^2 (3 pts), 16 mg/m^2 (4 pts), 30 mg/m^2 (5 pts), 45 mg/m^2 (11 pts), 60 mg/m^2 (6 pts) and 78 mg/m^2 (3 pts). Tumour types were: 6 breast, 5 ovary, 5 melanoma, 1 renal, 7 colorectal, 2 NSCLC, 2 pancreas, and 4 primary unknown. Initial doses were given at 28 day intervals with subsequent reduction to a 21 day cycle after 8 patients had been treated at 45 mg/m^2. A median of 2 courses was given (range 1–5). Haematological toxicity was mild. One patient experienced a grade 3 neutropenia and 2 patients grade 3/4 thrombocytopenia (toxicities at 45 mg/m^2). No grade 3/4 haematological toxicity was seen at 60 mg/m^2 or 78 mg/m^2. Grade 3 diarrhea (45 mg/m^2), nausea (45 mg/m^2) and mucositis (60 mg/m^2) were seen in 3 separate patients. We previously reported a 21–50% fall in GFR with repeated dosing. At 60 mg/m^2 the change in pretreatment GFR measured by ^{51}Cr-EDTA was between −11.9% and +23.8%. No alteration in serum creatinine was seen at any dose level. One patient (30 mg/m^2,