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A PHASE I AND BIOAVAILABILITY STUDY OF ORAL TOPOTECAN

J. Eckardt, H. Burris, J. Rizzo, S. Fields, G. Rodriguez, P. DelaCruz, S. Hodges, D. Von Hoff, J. Kuhn
The Cancer Therapy and Research Center and The University of Texas Health Science Center, 78229 San Antonio, Texas, U.S.A.

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

P. O'Dwyer[1], L. Pas-Arez[2], R. Kunka[3], D. DeMaria[1], J. Cassidy[2], S. Kaye[2], S. DePee[3], D. Littlefield[3], K. Selinger[3], P. Beranek[3], J. Graham[3], P. Wissel[3]
[1]*Fox Chase Cancer Center, Phila. PA, U.S.A.*
[2]*Western Infirmary, Glasgow, U.K.*
[3]*Glaxo, Inc. RTP, NC 27709, U.S.A.*

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)

P.A. Vasey[1], R. Duncan[2], S.B. Kaye[1], J. Cassidy[3]
[1]*CRC Department of Medical Oncology, Western Infirmary, Glasgow, U.K.*
[2]*London School of Pharmacy, 29/39 Brunswick Square, London, U.K.*
[3]*Department of Oncology, University of Aberdeen, U.K.*

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.

930 ORAL

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

R. Schnell[1], M.-T. Hatwig[1], A. Radszuhn[1], F. Cebe[1], S. Drillich[1], G. Schön[1], H. Bohlen[1], M.-L. Hansmann[2], J. Schindler[3], V. Ghetie[3], J. Uhr[3], V. Diehl[1], E.S. Vitetta[3], A. Engert[1]
[1]*Med. Universitätsklinik I*
[2]*Institut für Pathologie, Cologne, Germany*
[3]*Department of Microbiology and Cancer Immunobiology Center, UTSC, Dallas, Texas, U.S.A.*

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

N. Bailey, A. Humphreys, S. Laohavinij, M. Lind, L. Robson, A. Calvert
Cancer Research Unit, University of Newcastle upon Tyne, Newcastle, U.K.

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,

breast cancer) had a partial response of 6 weeks duration. The MTD has not been reached and the next dose escalation will be 100 mg/m^2. It is clear that coadministration of folic acid ameliorates the clinical toxicities seen with lometrexol.

932 POSTER

HIGH DOSE CONTINUOUS INFUSION (CI) IFOSFAMIDE WITHOUT HEMATOPOIETIC SUPPORT IN HEAVILY PRETREATED BREAST CANCER (BC) AND SARCOMA (S) PATIENTS

J. Bellmunt, A. Ribas, S. Casado, J. Albanell, J. Carulla, L.A. Solé
Hospital General Universitari Vall d'Hebron, Barcelona, Spain

Ifosfamide (IFO) is an oxazophosphorine with a different activity and toxicity profile than cyclophosphamide. Its use together with uroprotective agents has allowed safe administration and dose-escalation. We report the results of a phase II trial of IFO at high doses in heavily pretreated BC and S patients. IFO was administered in a 168 hour-CI through a central venous access, for a total dose of 14 g/m^2 q3w. MESNA was administered together at equimolar doses. Ondansetron, 8 mg/8 h po was used as antiemetic treatment. No hematopoietic support was used. We included 10 BC and 14 S patients with disease progression during salvage chemotherapy at conventional doses. Mean previous lines of therapy 3 (range 1–5), 20 had received previous treatment with conventional-dose cyclophosphamide or IFO. All had received previous adriamycin. Median age 44 (range 18–62), 12 males and 12 females. Median number of cycle 3 (range 1–8) for a total of 81 cycles of therapy. Worst WHO grade toxic reaction for each patient: grade III–IV leukopenia in 65%, grade III nausea and vomiting in 40%, grade III neurotoxicity in 5%, grade II nephrotoxicity in 5%. Neurologic and renal toxicity were reversible. 9 patients were admitted for neutropenic fever, with two documented septic episodes. Treatment had to be discontinued in 2 patients after 2 cycles (1 renal toxicity, 1 gastro-intestinal-GI-toxicity). 20 patients are evaluable for response (4 did not finish the first cycle of therapy, 3 for early disease progression, 1 for unacceptable GI toxicity). Partial responses in 2/8 (25%) BC, and in 3/12 (25%) S. No complete responses were recorded. 65% had disease stabilization, and 10% had disease progression. 3 with S and 1 BC underwent further high dose chemotherapy with transplantation after assessment of chemotherapy sensitivity with high-dose IFO. Median duration of response was 5 months. Median overall survival was 6 months (range 2–11+). In conclusion, CI of IFO for 168 hours is an active regimen in highly pretreated BC and S. The addition of hematopoietic growth factors and further antiemetic agents could improve the toxicity of this regimen. Additionally, this regimen could be combined with non-myelotoxic drugs.

933 POSTER

OXALIPLATIN (L-OHP®): GLOBAL SAFETY IN 682 PATIENTS (PTS)

S. Brienza[1], J. Vignoud[1], M. Itzhaki[2], A. Krikorian
[1]*Debiopharm, Villejuif, France*
[2]*Hôp. P. Brousse, Villejuif, France*

L-OHP® is a Dach platinum with significant activity in pretreated advanced colorectal cancer. In order to describe its safety profile, we gathered the individual data of 682 patients (pts) who received 4303 cycles (cy) from 9 studies (seven phase II and two phase III).

Treatment: L-OHP® was given as a single agent (SA, in 4 studies (40% of pts) and combined with 5-FU folinic acid (FFL) in 5 studies (60% of pts). L-OHP® was administered in 5 different schedules: 130 mg/sqm/d1 iv over 2 hrs q3 wks in 37% of pts, 130 mg/sqm/d1 iv over 6 hrs q3 wks in 5% of pts, 100–200 mg/sqm continuous infusion (CI) over 5 days q3 wks in 20% of pts and 100–200 mg/sqm chronomodulated (CM) on 5 days q3 wks in 38% of pts. *PT Characteristics:* Sex M/F: 63/37% PS (WHO) 0–1/2–3: 81/19%. Median age: 60 yrs. Tumor diagnosis: colorectal 80%, H&N 6%, melanoma 5%, other 9%. Pretreatment by chemotherapy (CT): 47%. Baseline abnormality grade (gr) 1–2: anemia 13%, WBC 3%, renal 2%, hepatic 88%, diarrhea 6%. *Methodology:* Separate univariate and multivariate analyses were performed for single agent and combination studies, influence of the following prognostic factors was sought: age, sex, PS, previous CT, modality, renal baseline status. Each toxicity was evaluated according to the overall incidence (gr 1–4), severity (gr 3–4) and baseline status. *Results (WHO and WHO modified scale):* No drug related toxic death occurred. Global results are shown in the following table.

Toxic effects	Incidence (gr 1–4)		Severity (gr 3–4)		Prognostic factors
	SA	FFL	SA	FFL	
Hematology	22%	35%	2%	6%	Sex:F-PS:2-3***
N-V*	65%	90%	11%	22%	None
Diarrhea	30%	85%	4%	25%	None
Neurologic**	80%	83%	3%	19%	Cumulative dose

*With prophylactic antiemetic treatment. **WHO modified scale. ***Anemia.

Sensitive peripheral neuropathy is the most frequent limiting toxicity. Grade III neurotoxicity (functional impairment) appears in 12% of the pts at a median dose of 900 mg/sqm (range: 200–2525). According to Kaplan–Meier model, the risk of developing a severe neurotoxicity is: 10% after 6 cy (780 mg/sqm) and 50% after 9 cy (1170 mg/sqm). Its reversibility was evaluated after discontinuation in 78% of pts with ⩾gr 2 neuropathy. Regression of symptoms was observed in 82% of these pts (median follow-up: 3–4 months) and disappearance for 41% of them (median follow-up: 6–8 months). Hematological and digestive toxicities were acceptable and caused discontinuation of the treatment in only 3 pts. Other severe toxicities were immediate intolerance (hypotension, faintness) in 1% of pts. There was no renal or auditive toxicity episode. *Conclusion:* Oxaliplatin can be administered safely by CI, CM or 2–6 hrs infusion at 130 mg/sqm q3 wks. Its association with 5-FU/folinic acid does not enhance its toxicity as it is very well tolerated.

934 POSTER

PACLITAXEL (P) AND EPIRUBICIN (E) IN ADVANCED BREAST (ABC) AND OVARIAN CANCER (AOC): A PHASE I STUDY

P.F. Conte, A. Michelotti, A. Romanini, E. Baldini, P.G. Giannessi, M. DaPrato, C. Tibaldi, M. Conti, A. Tognoni, B. Salvadori, A. Gentile[1], O. Biadi[2], M. Mariani[2]
U.O. Oncologia Medica Ospedale S.Chiara, Pisa
[1]*Bristol Myers Squibb*
[2]*Istituto di Cardiologia, Università di Pisa*

We have started a phase I study in ABC and AOC pts to determine the maximum tolerated dose (MTD) of P to be given with E. Up to now, 21 pts (10 MBC and 11 AOC) have been accrued. Patient characteristics: median age 59 y (36–71); median PS (ECOG) 0 (0–1); all MBC pts had received adjuvant chemotherapy and all AOC pts were pretreated with cisplatin regimens; 18 pts were pretreated with a cumulative E dose of 360 mg/sqm. P was given i.v. by a 3 hrs c.i. at 135 mg/sqm (9 pts); 155 mg/sqm (6 pts); 175 mg/sqm (5 pts) and 200 mg/sqm (1 pt). E was given at a fixed dose of 90 mg/sqm i.v. bolus. Courses were repeated every 21 days. All the pts have been submitted to a clinical and instrumental cardiological monitoring including: physical examination, EKG, EKG Holter, late potentials, transoesofageal electrophysiologic study, cardiac echo-doppler. 81 courses have been administered: 46 at level 1, 26 at level 2, 12 at level 3 and 1 at level 4. The main side effects was: G4 neutropenia in 57% of the courses lasting a median of 4 days (1–6). No cardiac toxicity has been observed; the median left ejection fraction was 59% at study entry and 54% after 7 courses (total cumulative dose of E = 990 mg/mq). Response rate was 62.5% in ABC and 44.4% in AOC. PE is an active regimen; the main toxicity is short-lasting neutropenia and the MTD has not yet been reached. The study is ongoing.

935 POSTER

A PHASE I STUDY OF THE COMBINATION OF DOCETAXEL (D) AND ADRIAMICIN (AD) IN FIRST LINE CT TREATMENT OF METASTATIC BREAST CANCER (MBC)

V. Dieras[1], G. Gruia[2], P. Pouillart[1], E. Cvitkovic[2], M. Gentin[3], N. Azli[3], A. Riva[3], J.L. Misset[2]
[1]*Institut Curie*
[2]*Hôpital Paul-Brousse*
[3]*Rhône-Poulenc Rorer, Antony, France*

The combination of D and AD is a logical attempt to optimize MBC therapy. The ongoing phase I trial has the objective to determine the DLT, MTD and RD in previously untreated pts with CT for MBC with measurable and/or eval disease receiving AD IV bolus followed by D 1 h IV infusion q3w. Prior Adjuvant CT with anthracycline (less than 300 mg/m^2) was allowed provided at least a ⩾12 month interval before study entry. Pts were required to have normal baseline LVEF monitored every 2 cycles. Prophylactic premedication is given with 3d. steroids (starting from d-1 8 mg every 6 hours) and Tanakan® from the day of 1st infusion. At least 3 pts are entered by dose level. The main toxicities are as follows: