Patients and Method: Within a Phase I-trial of the Arbeitsgemeinschaft Internistische Onkologie (AIO) the drug is currently tested for DLT and MTD. At present 17 patients have been treated up to a dose level of 60 mg/m^2 MTX-HSA once weekly up to 8 weeks.

Results: DLT has occurred, mainly stomatitis (CTC-Grade 2 or 3), beginning at the dose-level of 50 mg/m^2 once weekly. Monitoring of plasma MTX-HSA levels (modified EMIT, Syva Co., Paolo Alto, CA 94303) shows accumulation of the drug at a weekly application schedule. The terminal half-life of the drug is 15–19 days, AUC > 5000 μmol/l × h are achieved without toxicity. Tumor-response was seen in three patients: PR in one patient with renal cell carcinoma, MR in two patients with mesothelioma and renal cell carcinoma.

Conclusion: The MTD is not yet defined. The study will be continued with a bi-weekly application schedule.

1130 POSTER

Evidence for enhanced toxicity to CPT-11 in patients with Gilbert's syndrome: Two case reports

E. Wasserman[1], A. Myara[2], F. Lokiec[1], M. Ould Kaci[1], F. Goldwasser[1], E. Magherini[3], E. Cvitkovic[1], J.L. Misset[1]. [1]*SMST Hôp P. Brousse, Villejuif;* [2]*Lab. Biochimie St Joseph, Paris;* [3]*Rhône Poulenc Rorer, Montrouge, France*

CPT-11 acts as a prodrug in vivo, being converted to SN-38 by carboxylestearases. The topoisomerase I inhibition (antitumor activity) as the limiting toxicities are determined by free SN-38 concentration. Since glucuronidation represents the major detoxification pathway of SN-38, patients with a deficit in this enzyme's activity should have greater toxicity. We report here two cases of unexpected toxicity observed during an ongoing Phase I of the combination CPT-11/Oxaliplatin (L-OHP), where known glucuronidation deficiency was correlated with enhanced toxicity.

Patients and Methods: Patient A (a 49 year-old woman) and patient B (a 63 year-old woman), both with metastatic colon cancer progressed under previous fluoropyrimidine-based schedules. They had both been previously diagnosed as having Gilbert's syndrome and had no evidence of hemolysis.

After the first cycle of CPT-11/L-OHP was administered, they showed an increase of bilirubin (bil) in plasma (A: mainly unconjugated bil; B: conjugated and unconjugated bil). The bil increase began on days 2–3, maximal value on days 5–7, decreasing on days 9–13. The doses were A: 85/150 mg/sqm and B: 110/200 mg/sqm for L-OHP/CPT-11 respectively. Simultaneously to that reversible pattern of bil, patients A and B exhibited severe diarrhea and/or neutropenia in all of 12 cycles given (see table).

Pt/Cy	Baseline bil μmol/L (mean)	Max. bil μmol/L (mean)	Dose (mg/sqm) L-OHP/CPT-11	Limiting toxicities (grade 4)	AUC ng/ml/h CPT11/SN38/SN38G	Biliary index
A/10	27	60	85/150	diarrhea/ neutropenia	15386/419/784	8222
B/2	21	43	110/200	diarrhea/ neutropenia	29975/674/2843	7106

Conclusion: Pharmacogenetic differences in drug metabolism contribute to treatment related toxicities Low SN-38 glucuronidation should account for the enhanced toxicity evidenced by two patients with Gilbert's syndrome.

1131 POSTER

Phase I Study of paclitaxel (P) combined with 14-day topotecan (T) Continuous IV (CIV) infusion in previously treated and untreated patients (PTS)

H. Hochster, A. Chachoua, J. Sorich, C. Wasserheit, B. Taubes, A. Friedberg, S. Arbuck, J. Speyer. *Kaplan Cancer Center, NYU Medical Center, NY, NY, NCI, CTEP, Bethesda, MD, USA*

Purpose: 21-day CIV with T appears to have at least equal activity to the daily × 5 schedule with considerably less myelosuppression. This toxicity (tox) profile for combination therapy prompted a Phase I study to combine P 3-hr infusion q 21 days with 14-day T CIV. Preliminary results were previously reported (Proc ASCO, 1995).

Methods: Pts met typical Phase I criteria. P was given as a 3 -hr infusion followed by T as a 14-day infusion using an ambulatory CADD pump. Cassettes were changed weekly.

Results: The initial cohort consisted of 11 pts (8 F, 3 M) with adequate organ function, median PS 1, median age 63 y, and median of 2 prior chemo regimens. Initial dose level was P 135 mg/m^2 with T 0.3 mg/m^2/d × 14 d CIV. One of pts at this level had a maximum of gr 3 ANC tox and dose was escalated to P 135 and T 0.4, which gave 6/6 pts gr 3 WBC, 2/6 pts gr 3 ANC tox (no plt tox), without clinical sequlae. The study was revised to include pts without prior chemo and a new definition of MTD requiring gr 4 ANC > 5 d or neutropenic fevers/sepsis. At the same time doses were escalated to P 150 and T 0.4. 1/4 pts developed gr 3 ANC tox. At the current dose level of P 175 and T 0.4, 1 pt had no heme tox. Non-heme tox included: N/V gr 1 = 9 pts, gr 2 = 1 pt; diarrhea gr 1 = 4 pts, gr 2 = 2 pts; myalgias gr 1 = 6 pts, gr 2 = 3 pts; neuropathy gr 1 = 1 pt, gr 2 = 2 pts, gr 3 = 1 pt; fever gr 2 = 6 pts. In the initial cohort, 1 CR + 1 PR (ovarian CA) + 3 SD/11. The CR pt remained in remission 1 y before relapse and a second CR. In the second cohort, 1 PR (NSCLC) + 1 SD/5. Accrual is ongoing at the 175/0.4 level to determine MTD with full results to be presented.

Conclusion: This regimen appears to allow a well-tolerated means of maintaining both P and T dose intensity and should be tested in the Phase II setting. (Supported by CA16087, R01 CA56129 with thanks to CTEP NCI. Also supported by SmithKline Beecham.)

1132 PUBLICATION

Hormonal effects of MPV-2213ad, a novel, competitive aromatase inhibitor in healthy male volunteers. A phase I study

O. Ahokoski[1,2], K. Inala[3], R. Huupponen[1], K. Halonen[5], E. Salminen[2], H. Scheinin[1,4]. [1]*Department of Pharmacology and Clinical Pharmacology, University of Turku; The Clinical Pharmacology Unit;* [2]*the Departments of Oncology and Radiotherapy;* [3]*Central Laboratory;* [4]*Anesthesiology, Turku University Central Hospital;* [5]*Anticancer research, Orion Corporation, Orion Pharma, Turku, Finland*

Aim: The purpose of this open, dose-escalation study was to investigate the hormonal effects, safety and tolerability of MPV-2213ad, a new selective aromatase enzyme inhibitor.

Methods: Thirty nine healthy male volunteers were entered into the study. MPV-2213ad was given as single oral doses of 0.003, 0.03, 0.3, 3, 9, 30, 100 mg to three subjects at each dose level, ten subjects received 300 mg and eight subjects the 600 mg dose. Blood specimens for hematological, biochemical and endocrine analysis were taken frequently during the first 24 h and 2, 4, 7, 14 and 21 days after drug administration.

Results: MPV-2213ad induced a dose-dependent decrease in serum estradiol levels. The maximal reduction of serum estradiol levels was 83% after the 300 mg dose, the highest dose did not give additional decrease. After doses between 0.3 and 30 mg the estradiol suppression was 58–65%. The suppression lasted longer with higher doses of MPV-2213ad, a return to baseline levels was observed within 4 days after all doses. Significant increases in the serum concentrations of testosterone, androstenedione, 17-OH-progesterone, LH and FSH were observed. There were no signs of adreno-cortical suppression. The drug was well-tolerated. The adverse effects were mild or moderate and consisted of hot flushes, mild vertigo, nausea and gastro-intestinal discomfort.

Conclusion: This phase I study introduces a new competitive aromatase inhibitor. The results indicate that MPV-2213ad is a selective and well-tolerated compound with a significantly suppressive effect on serum estradiol.

1133 PUBLICATION

Phase IB study of methoxymorpholinodoxorubicin (PNU 152243; FCE 23762) administered in a 3 or 4 weekly schedule

P.G. de Takats[1], D. Dunlop[2], S.B. Kaye[2], D.W. Fyfe[1], P. Baker[1], M.A. Pacciarini[3], O. Valota[3], D.J. Kerr[1]. [1]*University of Birmingham CRC Institute for Cancer Studies;* [2]*Beatson Oncology Centre, Glasgow, UK;* [3]*Pharmacia & Upjohn, Milan, Italy*

The lipophilic anthracycline, FCE 23762, has been shown to possess broad spectrum antitumour activity, including efficacy against multidrug resistant tumours. It appears to be activated in vivo, with resulting potency 80-fold greater than doxorubicin. The initial phase I study defined the MTD as 1.5 mg/m^2/3 weeks, but heavily pretreated patients experienced more myelosuppression at the recommended dose of 1.25 mg/m^2 than did previously untreated patients. We have studied the feasibility of administering 1.25 mg/m^2 (bolus IV) either 3 or 4 weekly in untreated cancer patients.

15 patients were entered on the 3 weekly schedule (5 renal, 3 non small cell lung cancer [NSCLC], 5 colorectal, 1 head and neck, 1 unknown origin). A further 9 patients were entered on the 4 weekly schedule (1 renal, 3 NSCLC, 3 colorectal, 2 unknown origin). Toxicity by CTC indicated no cardiotoxity; 3 weekly treatment was associated with transient grade II/III hepatic transaminitis in 10% and grade III/IV nausea/vomiting in 12% of cycles, but was absent in the 4 weekly schedule. Grade III neutropenia and

thrombocytopenia was not seen in cycle 1, but occurred in around 10% and 5% of subsequent cycles, respectively, irrespective of treatment schedule. Both nadirs were on day 22, with need for dose delay suggesting that the optimum schedule for FCE 23762 administration is every 4 weeks.

By WHO criteria, no partial responses were seen. However, 3 patients with liver metastases (2 renal, 1 colorectal primary) showed early radiological and post mortem evidence of response. In view of suggested efficacy against liver disease, a phase I study is currently underway, administering FCE 23762 directly into the hepatic artery of patients with primary and secondary liver cancers.

1134 PUBLICATION

Phase I and pharmacokinetic (PK) study of irinotecan (CPT-11) and cisplatin in patients with solid tumors: Preliminary results

M.J.A. de Jonge[1], A. Sparreboom[1], A.S.Th. Planting[1], M.E.L. van der Burg[1], P. de Bruijn[1], E. Brouwer[1], V. van Beurden[1], M.R. van Duijn[1], Ch. Jacques[2], J. Verweij[1]. [1]*Department of Medical Oncology, Rotterdam Cancer Institute, 3075 EA Rotterdam, The Netherlands;* [2]*Rhône-Poulenc Rorer, Antony, France*

Purpose: Irinotecan is an inhibitor of topoisomerase-1, showing clinical antitumor activity in a wide variety of solid tumors. Cisplatin is one of the most commonly used cytotoxic drugs for solid tumors. According to their mode of action, the combination of these two drugs may act synergistically. We perform a phase 1 study with a combination of the two drugs.

Methods: Patients eligibility includes no prior treatment with topoisomerase 1-inhibitors and cisplatin; no more than 1 prior combination chemotherapy regimen or 2 single agent regimens and abscence of bowel obstruction or chronic diarrhea. The other criteria were as usual for phase 1 studies.

Treatment consisted of irinotecan given as a 90-minutes transfusion at t = 0 and cisplatin given as a 3-hr infusion starting at t = 90 minutes. Cycles were repeated every 3 weeks. Toxicity was scored according to CTC-criteria, anti-tumor activity according to WHO-criteria.

Results: Up till now 16 patients (pts), 12 males and 4 females, median age 53 years (range 42–68 y), median performance score 1 (range 0–1), are entered and 9 are evaluable for PK. Cisplatin doses ranged from 60–80 mg/m^2, irinotecan doses from 175–230 mg/m^2. 51 Courses have been evaluated. An acute cholinergic syndrome during the infusion of irinotecan was observed in 20%, requiring in only one pt therapy with atropine. Major toxicities consisted of leucopenia 82% (grade 3–4 37%) and neutropenia 76% (grade 3–4 59%) with only 5% related infections. Diarrhea occurred in 29% and was severe in 8% (grade 2–3). In case of diarrhea, immediate therapy with loperamide was started. Other toxicities included nausea 63% (grade 3 4%), vomiting 49% (grade 3–4 4%), alopecia 67%, renal toxicity grade 1 8% and neurotoxicity grade 1–2 14%. PK parameters were similar for CPT-11, its active metabolite SN-38 and cisplatin between the various doses. 2 Partial responses were observed.

Conclusion: Despite the fact that already high doses of both drugs are used, dose limiting toxicity has not yet been reached.

1135 PUBLICATION

Clinical and pharmacokinetic phase I study with taxol® given as short 1-hour intravenous infusion

K. Mross[1], B. Häring[1], B. Hauns[1], H. Maier-Lenz[1], T. Bauknecht[2], H.G. Meerpohl[3], K. Diergarten[4], C. Unger[1]. [1]*Tumor Biology Center at the University Freiburg;* [2]*University Hospital Freiburg;* [3]*Vincentius Hospital Karlsruhe;* [4]*Bristol Myers Squibb München, Germany*

Purpose: To study the toxicity, pharmacokinetics and anti-cancer effects of a one-hour infusion of paclitaxel (Taxol®).

Method: Thirty-four advanced cancer patients (lung, breast and ovarial cancer) were enrolled into this study. The drug dose started at 150 mg/m^2 and was escalated to 250 mg/m^2. The drug was given as 1-hour infusion in 3-week intervals with the well-known pre-medication.

Results: The dose limiting toxicity was reversible neurotoxicity. Stable disease and partial regressions were seen in 40% of all patients, the other progressed. The c(t)-curves were best described by a two-compartment model. The pharmacokinetics was linear up to 225 mg/m^2 the highest dose level showed some deviation from linearity.

Conclusions: The dose recommendation for phase II/III studies is 225 mg/m^2 which showed anticancer efficacy and nearly no myelotoxicity.

1136 PUBLICATION

Dose finding and pharmacokinetic (PK) study of daily oral idarubicin (IDA) in metastatic breast cancer (MBC)

R. Sorio, G. Toffoli, I. Robieux, G. Rimondi, P. Aita, G. Corona, D. Crivellari, A.M. Colussi, S. Tumolo. *Experimental and Clinical Pharmacology Lab, Div Medical Oncology CRO, Istituto Tumori Centro Europeo, 33081 AVIANO, Italy*

The anthracyclin IDA is under investigation for solid tumors. The oral route allows prolonged low dose therapy. We performed a dose-finding and PK study of daily oral IDA with intrapatient escalation in patients with metastatic breast cancer (MBC).

Inclusion Criteria: MBC pts, pretreated with anthracyclines; PS 0–2; normal liver function test; left ventricular ejection fraction >50%. **Treatment Plan:** IDA (1 mg capsules) orally twice daily for 21 days every 4 weeks. Treatment was continued at escalating doses by 1 mg steps until progression or intolerance.

PK Methods: IDA and active metabolite IDOL were measured by HPLC and PK was studied using non-compartmental equations.

Results: 18 pts have been enrolled: mean age 57 ± 10 yrs and median PS = 1.

Daily dose	2 mg	3 mg	4 mg	5 mg	6 mg	7 mg	total
# new (total) pts	7 (7)	4 (9)	1 (6)	3 (4)	2 (5)	1 (3)	18
toxicity (ANC)	0	1 (G4)	0	0	1 (G2)	NA	1
# cycles with PK	7	9	6	3	1	NA	26

Treatment was well tolerated in all but one pt (300 ANC at day 28). We observed 1 PR and 4 NC in 12 evaluable pts.

PK Results: half-life 14 ± 3 hrs and 41 ± 21 hrs for IDA and IDOL respectively; IDA systemic clearance 1109 ± 571 l/hr and distribution volume 5160 ± 670 l. Mean IDOL/IDA ratio was 10. The pt with G4 tox had a very high systemic exposure (SE) to IDOL (6.7 times higher than other pts).

Conclusions: MTD has not been reached and accrual is ongoing. The PK suggest a clinically relevant role of IDOL in toxicity. PK guided phase I studies should aim at defining MTSE rather than MTD.

1137 PUBLICATION

Binding of toremifene to human serum proteins: Study on potential interactions between toremifene and other highly protein-bound drugs *in vitro*

S. Laakso, M. Anttila. *Orion Corporation, Orion Pharma, R&D, Turku, Finland*

Purpose: This study was designed to identify binding interactions in human serum between toremifene and a number of other highly protein-bound reference drugs at therapeutic concentrations.

Methods: Blank serum taken from human volunteers after an overnight fast was pooled and spiked with the drug alone and together with toremifene. To achieve an appropriate drug concentration and radioactivity in the samples both unlabelled and labelled or (^{3}H or ^{14}C) compounds were added. The unbound fraction of each radiolabelled compound was measured in the supernatant after ultracentrifugation using liquid scintillation counter; experiments were conducted in triplicate.

Results: The unbound fraction of diltiazem, salicylic acid, indomethacin, warfarin, and glibenclamide in human serum were 21.6%, 12.3%, 1.2%, 0.55%, and 0.34%, respectively, and was not affected by toremifene. The unbound fraction of toremifene was 0.13%, and was not affected by the reference drugs.

Conclusion: Toremifene is extensively bound to serum proteins and does not appear to displace, or be displaced by the selected other highly protein-bound reference drugs.

1138 PUBLICATION

Is gamma linolenic acid potentially an effective intravesical agent for superficial bladder cancer? *in vitro* cytotoxicity and *in vivo* tolerance studies

L.Z. Solomon, A.M. Jennings, B. Birch, A.J. Cooper. *University Departments of Surgery and Urology, General Hospital, Southampton, UK*

Purpose: Gamma linolenic acid (GLA) is selectively cytotoxic to tumour cells on prolonged exposure *in vitro*. Its efficacy in vivo depends on topical application in high concentration. These conditions obtain in intravesical