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