

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

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**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 I 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 absence of bowel obstruction or chronic diarrhea. The other criteria were as usual for phase I 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<sup>2</sup>, irinotecan doses from 175–230 mg/m<sup>2</sup>. 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

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**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 ovarian cancer) were enrolled into this study. The drug dose started at 150 mg/m<sup>2</sup> and was escalated to 250 mg/m<sup>2</sup>. 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<sup>2</sup> the highest dose level showed some deviation from linearity.

**Conclusions:** The dose recommendation for phase II/III studies is 225 mg/m<sup>2</sup> 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)

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The anthracycline 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*

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**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 (<sup>3</sup>H or <sup>14</sup>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

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**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

therapy for superficial bladder cancer, except for the length of exposure. This study measures the toxicity of short GLA pulses on a cultured bladder cancer cell line and the tolerance of rat bladders to intravesical dosage.

**Methods:** a) The MGHU-1 anchorage dependent bladder cancer cell line was pulsed with meglumine-GLA (MeGLA) between 2 & 1000 µg/ml for up to 2 hours in 96-well plates. The MTT biomass assay was used to assess cytotoxicity 5 days later. b) Bladder histology was performed on rats given 0.3 ml, 2.5 mg/ml MeGLA intravesically. The drug was retained for 1&2 hours.

**Results:** Maximum cell kill was seen at drug exposures of 1 hour or more and over 125 mg/ml. Intravesical exposure to >10× this concentration of drug caused minimal histological damage, which resolved within two weeks.

**Conclusion:** GLA is toxic to bladder cancer cells given short exposures. It is well tolerated in an *in vivo* model. A clinical application is feasible.

1139

## PUBLICATION

### Vinorelbine/gemcitabine in advanced non-small-cell lung cancer (NSCLC): A phase I trial

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**Purpose:** We performed a phase I dose-escalation trial of intravenous vinorelbine/gemcitabine in patients (pts) with advanced NSCLC.

**Patients:** Previously untreated pts (N = 33) were treated on days 1, 8 and 15. This cycle was repeated on day 29 (= day 1 of next cycle). Dose-limiting toxicity (DLT) was defined as severe myelotoxicity and/or any WHO Grade 3/4 non-hematologic toxicity.

**Results:** Toxicity for evaluable (2 cycles except in the case of DLT) pts and responses (CR+PR) for all entered pts are summarized below.

VIN mg/m <sup>2</sup>	GEM mg/m <sup>2</sup>	Eval.(all) pts	WBC WHO 3/4	DLT	CR+PR
10	600	3 (4)	0/0	0/3	0/4
15	800	3 (5)	0/0	0/3	0/5
20	800	3 (4)	0/0	0/3	0/4
20	1000	3 (3)	0/0	0/3	2/3
25	1000	6 (8)	4/0	1 cardiac/6	3/8
25	1200	3 (6)	2/0	1 pulmonary/3	1/6

**Conclusion:** The maximum tolerated dose has not been reached up to 25 mg/m<sup>2</sup> vinorelbine plus 1000 mg/m<sup>2</sup> gemcitabine.

1140

## PUBLICATION

### Phase III study of taxol/ifosfamide/cisplatin (TIP) combination chemotherapy (CMT) in advanced solid tumors (ST)

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In the present study, we evaluated the TIP combination in the outpatient setting in pts with a variety of advanced ST. Pts were entered into the following dose levels (DL): DL-I: T = 135 mg/m<sup>2</sup> day (d) 1-(1 hr), I = 2.25 g/m<sup>2</sup>/d d1-2 (total = 4.5), P = 40 mg/m<sup>2</sup>/d d1-2 (total = 80), DL-II: T = 175 d1, I = 2.25 d1-2, P = 40 d1-2, DL-III: T = 175 d1, I = 2.25 d1-2, P = 50 d1-2 (total = 100), DL-IV: T = 215 d1, I = 2.25 d1-2, P = 50 d1-2 and DL-V: T = 215 d1, I = 3.0 d1-2 (total = 6.0), P = 50 d1-2. G- or GM-CSF was given d5-14. 23 pts have entered: 5 at DL-I, 8 at DL-II, and 9 at DL-III. 1 pt with relapsed germ-cell tumor entered directly at DL-V to receive intensive P and I-based CMT. Histologies: 13 non-small cell lung (NSCLC), 6 ovarian (OC), 2 cervical Ca, 1 GCT, and 1 nasopharyngeal Ca. All but 5 had 2-8 cycles of prior CMT (no taxanes or I; P allowed) and progressed 6 wks after last CMT cycle. Characteristics: 13 males/10 females, age 25-67 yrs (median = 55), PS 0-2. The regimen was tolerated with outpatient administration in 15/23 pts. 21 pts are evaluable for toxicity. 1 pt died from PD prior to cycle 2. Toxicities: Gr 4 neutropenia for ≤5 days: 9 pts; 2 episodes of febrile neutropenia at DL-III and DL-V. Gr3/4 thrombocytopenia was seen in 8/2 pts. The MTD has not yet been reached. Pts are currently accrued at DL-IV and V. 9/21 PRs were seen (42%).

**Conclusion:** TIP combination appears to be feasible in the outpatient setting; phase II studies are planned in NSCLC, OC, etc, after the MTD is defined.

1141

## PUBLICATION

### Phase I dose finding study of irinotecan (CPT-11) over a short i.v. infusion combined with a fixed dose of 5-fluorouracil (5-FU) protracted continuous i.v. infusion in patients with advanced solid tumours

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**Purpose:** This ongoing Phase I study is designed to define an effective combination schedule of CPT-11 with 5-FU in patients with advanced adult solid tumours.

**Methods:** CPT11 is administered over a 90 min iv infusion on day 1 with a dose escalation schedule of 150, 175, 200, 250, 300 and 350 mg/m<sup>2</sup> q3w. 5-FU, in a fixed dose of 250 mg/m<sup>2</sup>/d, is administered as a protracted continuous iv infusion over 14 days, q3w. Pharmacokinetic (PK) parameters are also evaluated.

**Results:** Since June 1996, 16 patients were treated of whom 14 are evaluable for toxicity. Patients characteristics: median age 53 years (38-65); median PS 1 (0-2); sex: M/F 15/1; primary site: colorectal 5, oesophagus 2, head & neck 3, kidney 1, prostate 1, unknown primary 1, pancreas 1, small bowel 1, stomach 1. One partial response and various stabilisations were observed.

Dose (CPT11/5-FU)	N Patients.	N Cycles	Toxicity
Level 1: 150/250	3	10	No DLT
Level 2: 175/250	4	14	No DLT
Level 3: 200/250	3	7	No DLT
Level 4: 250/250	3	7	No DLT
Level 5: 300/250*	3( 2 pts. too early)	3	Grade 4 Neutropenia

**Conclusion:** Preliminary analysis shows this combination to be well tolerated. Study is ongoing, as maximum tolerated dose has not yet been reached at level 4.

1142

## PUBLICATION

### Abdominal and pelvic stop-flow (hypoxic, chemotherapeutic loco-regional treatment): Preliminary report of a phase I study

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**Purpose:** To establish the MTD, DLT and a safe dose for phase II study in stop-flow, a new loco-regional treatment with percutaneous double-balloon catheters, stop of blood flow and administration of high dose of Mitomycin-C (MMC) and Adriamycin (ADM), we started a phase I study.

**Methods:** From November 1995 to January 1997, were treated 23 patients, 8 pelvic and 15 abdominal, M/F 16/7, with histologically confirmed diagnosis of advanced neoplasms, unresectable or pretreated with standard chemotherapy. Dose escalation was: I° level MMC 15 mg/m<sup>2</sup> and ADM 75 mg/m<sup>2</sup>; II° level MMC 20 mg/m<sup>2</sup> and ADM 90 mg/m<sup>2</sup>; III° level Mit-C 25 mg/m<sup>2</sup> and ADM 120 mg/m<sup>2</sup>.

**Results:** MTD and DLT were found both at III° level. Myelotoxicity grade IV was observed at III° level. Gastrointestinal toxicity grade III was reported at III° level. One patient had a reversible deep vein thrombosis, another patient had acute tubular necrosis reversed after 20 days. One case of paraparesis reversed after 4 days, was registered. No death related to procedure was reported. 5RP were observed in 10 pts evaluable. Accrualment is ongoing to establish the safe dose for phase II study.

**Conclusions:** Stop-Flow seems to be a new feasible and safe loco-regional treatment and the complete resolution of symptoms as pain encourages to continue this study and to promote a phase II study.