Aim of the Study: We prospectively studied circulating T, N-demethyl T, N-dedimethyl T and 4-hydroxy T (D-T, DD-T and 4-OH-T) that to be matched with lipids, coagulation, blood counts, steroid hormone binding globulin (SHBG), various hormones, vaginal karyopyknotic index (KPI) (our previous studies BMJ ii: 1351–2, 1977; Cytopatol 9: 263–270, 1998) and transvaginal ecosonography endometrial morphology.

Patients were 85, consecutively enrollrd after radical surgery for M_0PBC, and given adjuvant T 20 mg/day for 5 years.

Results: T induces most of its agonist estrogen-like effects within 2 w.s therapy. A steady state of the biological events is reached in about 4 w.s and persists up to 60 mo.s. Cholesterol, LDL-C, HDL-C, LDL-C/HDL-C ratio, apolipoprotein B/apolipoprotein A ratio, fibrinogen and antithrombin III activity dropped from 2 w.s to 60 mo.s. HDL-C was unchanged, SHBG and KPI increased early, while FSH, LH and prolactin decreased. A late rise of Hb, PCV occurred from the 18th mo. Platelets were lower from the 4th w (all quoted results: $p \leq 0.005$). Plasma concentration of T and its metabolites shows interpersonal variations; the steady state was reached at the 4th w. Positive relations ($p \leq 0.005$) existed between 4-OH-T and fibrinogen and KPI, inverse relation between 4-OH-T and antithrombin III, D-T and fibrinogen, DD-T and fibrinogen. Agonistic properties are mainly exerted by the three metabolites. Further analyses is ongoing.

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Pharmacokinetics (PK) of irofulven using two different intermittent dosing schedules as a 30 minute (MIN) infusion in advanced solid tumors (AST): Preliminary data

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Purpose: Irofulven, an acylfulvene analog of illudin S, has shown promising anti-tumor activity during preclinical/clinical development, with delayed thrombocytopenia, severe asthenia and nausea/vomiting as treatment-limiting toxicities (tox). PK analysis of the 5 min daily × 5 or intermittent weekly dosing q3 or 4w schedules (sch) has shown a short mean plasma half-life ($t_{1/2}$) range: 4–6 min, with a large interpatient (pt) variability. A 30 min administration corresponds to approximately 5 $t_{1/2}$. Therefore, by the end of a 30 min infusion, a steady state will be reached. Within the ongoing Phase I study, we decided to use the 30 min infusion to improve the PK and pharmacodynamic (PD) analyses and to investigate a possible correlation between observed tox and Cmax.

Methods: Pts with AST were treated with the same schedules (sch) previously explored with the 5 min infusion duration (B: D1, 8, q3w and C: D1, 15 q4w) using the following dosing levels (DL in [*mg/m²/d*]). Sch B: DL2 [*18*], DL3 [*21*]; Sch C: DL2 [*24*], DL3 [*28*]. During each pt's first 3 infusions, 10 plasma samples were collected up to 5 hours post-infusion. As of 04/2001, 24 pts were included in DL2 and DL3 of both sch.

Results: PK analysis has been performed for day 1 in the first 17 pts. Total body clearance appeared stable up to 28 mg/m².

Dose mg/m²	Sch (DL)	N eval. pts	Cmax ng/ml	AUC ng/mlxh	Clearance l/h/m²	$T_{1/2}$ beta min
18	B (DL2)	7	112 ± 58	38.8 ± 18.1	568 ± 279	7.1 ± 3.6
21	B (DL3)	2	115 ± 4	35.9 ± 1.4	586 ± 23	1.9 ± 0.1
24	C (DL2)	7	202 ± 181	68.7 ± 61.6	532 ± 293	8.5 ± 6.8
28	C (DL3)	1	214	70.3	398	4.7

Conclusions: Preliminary results show that AUCs and total body clearances are similar when irofulven is administered as a 5 or a 30 minute infusion, despite its short terminal half-life. Fully updated PK analysis and the PK/PD relationships will be presented.

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Pharmacokinetic interactions between gemcitabine (GEM) and vinorelbine (VNR) in patients with advanced stage solid tumors

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Purpose: GEM and VNR are both active as single agents in patients with advanced stage of solid tumors. Because of their different mechanism of action, good tolerability and feasible administration on an outpatient basis they should be an interesting combination for palliative chemotherapy. The aim of this study is to determine possible pharmacokinetic interactions between GEM and VNR.

Methods: A total of 11 patients with advanced non small cell lung cancer or metastatic breast cancer were treated with GEM (1h i.v. infusion, 1000 mg/m2) followed by VNR (10 min i.v. slow bolus, 25 mg/m2) on days 1, 8, every 3 weeks; 5 patients received single-agent GEM (1h i.v. infusion, 1000 mg/m2) as a control group. GEM and VNR were measured in blood samples taken at several time points after the starting of treatment and immediately added with enzymatic inhibitor of deaminase THU. Plasma levels were quantified by liquid extraction followed by HPLC analysis and pharmacokinetic data were processed by KineticaTM 1.1 computer program

Results: In the schedule GEM+VNR average Cmax of GEM was 26278±4671 ng/ml, AUC=20305±3111 ng/ml/h, Cltot=75,48±14,56 l/h, t1/2alfa=5,1±5,3 min;t1/2beta=18,2±3,4 min. The steady state was reached about 30 min after the beginning of administration; Cmax of VNR was 813±387 ng/ml, AUC=224±75 ng/ml/h, Cltot=192,74±72,51 l/h; Cmax of single-agent GEM was 29295±5681 ng/ml, AUC=24327±7346 ng/ml/h, Cltot=75,20±17,78 l/h, t1/2alfa=3,0±5,1 min, t1/2beta=20,0±5,2 min.

Conclusions: Cmax, AUC and Cl values of GEM followed by VNR agreed with the values shown in monotherapy; Cp/t curve for GEM in combination was best described by a biphasical model with a rapid distribution and elimination. Cp/t curve for VNR showed rapid distribution; moreover, interpatient variability was important for all parameters in accordance to the literature data; these preliminary data have shown that treatment with GEM+VNR do not alter the pharmacokinetic behaviour of both drugs compared with single agent therapy. Further investigation is needed to relate pharmacokinetic data to toxicity of the treatment.

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Pharmacokinetics of escalating doses of CCI-779 in combination with 5-fluorouracil and leucovorin in patients with advanced solid tumors

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Purpose: To evaluate the pharmacokinetics of 5-fluorouracil (5-FU) and CCI-779, administered in combination to patients with advanced solid tumors.

Methods: Weekly treatment spanned 6 weeks of a 7-week cycle. During day 1 of each treatment cycle, a 1 hour intravenous (IV) infusion of 200 mg/m2 leucovorin (LV) was followed by a 24 hour continuous infusion of 2600 mg/m2 5-FU. Starting on cycle1/day 8, 15 to 75 mg/m2 of IV CCI-779 preceded LV/5-FU treatment. Concentrations of 5-FU were measured throughout the 24 hour infusion period in cycle 1/weeks 1, 2 and 4; CCI-779 and its primary metabolite sirolimus (rapamycin) were followed for 8 days during cycle 1/weeks 2 and 4. Parameters were derived using noncompartmental methods.

Results: For 15 patients, mean±SD steady-state 5-FU plasma concentration was 667±202 ng/mL (Week 1 without CCI-779) and 666±248 ng/mL (Week 2 with CCI-779); mean clearance (CL) was 325±113 L/h (Week 2). For 13 patients, mean CCI-779 CL increased with increasing dose (13 L/h [low dose] to 41 L/h [highest dose] (CV ~ 30%). Mean half-life was 17±4 hours. The mean ratio of sirolimus-to-CCI-779 AUC was 2.4 to 3.8. No period effects were observed.

Conclusion: Inclusion of CCI-779 in the standard 5-FU/LV regimen did not affect 5-FU pharmacokinetic disposition, nor did 5-FU change CCI-779 pharmacokinetic parameters.