G 3 peripheral neuromotor toxicity occurred in 1/6 pts at 70 mg/m², 1/3 pts at 90 mg/m², 2/6 pts at 120 mg/m² and 1/3 pts at 160 mg/m². At present, 1 partial response (PR) and 2 minimal responses (MR) were observed: 1 MR at 90 mg/m² (vulva), 1 MR at 120 mg/m² (renal cell) and 1 PR at 120 mg/m² (mesothelioma).

Conclusions: The Maximum Tolerated Dose of L administered q 21 d is 120 mg/m² with peripheral neurotoxicity as Dose Limiting Toxicity. The recommended dose for Phase II trials is currently being established. L has antitumor activity and warrants further evaluation.

1107 ORAL

Phase I and pharmacokinetic study of ecteinascidin-743 (ET-743) given as a one hour infusion every 21 days

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Introduction: ET-743 is a novel tetrahydroisoquinolone isolated from a Caribbean tunicate. ET-743 exerts antitumour activity as a DNA minor groove interacting agent. ET-743 exhibits potent *in vivo* activity in human xenograft models. Dose-limiting toxicities in all species were hepatotoxicity and myelotoxicity.

Aims and Methods: Phase I study to determine the safety and pharmacokinetics of ET-743 given i.v. in 250 mls over 60 minutes every 3 weeks. Starting dose of 50 μg/m² represents (<1/10 mouse LD_{10}) with escalation according to a modified Fibonacci scheme.

Results: At present, the 50, 100, 200 and 330 μg/m² dose levels are evaluable. Twelve patients (7 M, 5 F), median age 60.5 (range 30–77) with refractory solid tumours received 38 cycles of ET-743 (median 2.5 range 1–7). ET-743 has been well tolerated with no dose-limiting toxicities. At ≥100 μg/m², 4 pts had reversible elevation of serum transaminases (CTC grade 1/2). One pt, who refused antiemetics, had grade 3 vomiting. Preliminary pharmacokinetic data show ng/ml concentrations of ET-743 at doses ≥100 μg/m² measured by HPLC.

Conclusions: ET-743 is tolerated at doses up to 330 μg/m² and this achieves detectable plasma levels. At a dose approximating to the MTD in preclinical studies there have been only minor, transient changes in liver tests. Four patients remain on therapy and accrual continues at 440 μg/m².

1108 ORAL

Phase I study of weekly cisplatin (P) and weekly or four weekly taxol (T) in patients with advanced ovarian cancer

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Purpose: Weekly P combined with oral VP16 is highly active in 2nd line therapy in ovarian cancer (OC) (ASCO '96 abstr 772). T is more active than VP16 in patients (pts) with recurrent OC. Because of this we performed a phase I study investigating whether P could be combined with either weekly or 4-weekly T.

Methods: Nine pts with primary and 15 with recurrent/progressive OC were treated with 2 cycles of induction therapy with P 70 mg/m² on day 1, 8 and 15 combined with either T on day 1, 8, 15 (T dose 60–90 mg/m²) or T on day 1 (T dose 135–200 mg/m²), full cycle repeated day 29. followed by 6 cycles T175 mg/m² and P75 mg/m² q 3wks.

Results: 23 Pts are presently evaluable for induction therapy. One pt stopped therapy after the 5th P administration because of an increase of neurotoxicity from grade 1 to 3. All other pts received 2 full cycles. Toxicity and response are summarized in the table.

T (mg/m²)	P (mg/m²)	N Pts/ cycles	Worst toxicity CTC grade per cycle/pts*													
			WBC		Gran			Pts		N/V		nephro		neuro*		Response
			2	3	2	3	4	2	3	2	3	1	2	1	2	CR	PR
T weekly N = 11																	
60	70	3/18	5	2	6	4	0	0	2	0	1	8	0	2	0	1	2
70	70	3/18	4	1	7	1	0	0	0	1	0	1	0	1	0	1	2
80	70	5/30	7	5	2	6	0	0	0	9	2	8	1	3	0	2	2
T 4 weekly N = 12																	
135	70	3/18	4	0	7	2	0	0	0	4	0	3	0	2	0	0	3
150	70	4/23	4	3	3	4	2	0	1	10	0	5	0	2	1	2	2
175	70	3/18	4	1	3	1	1	0	0	2	0	2	0	2	0	0	3
200	70	2/12	3	3	0	4	1	1	0	1	0	3	0	0	1	1	0

1109 ORAL

Amifostine (AMI) differently influences pharmacokinetics (PK) of selected cystostatic agents (CY)

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Purpose: For AMI, besides nephro- myeloprotection, reduction of anthracycline induced cardiotoxicity, Mitomycin C (MMC) induced thrombopenia and taxanes related neurotox. have been described in vitro or clinically. AMI has also been found to alter PK of platinum agents and doxorubicin. Therefore a potential influence of AMI on PK of MMC, Epirubicin (EPI), Paclitaxel (PAC) and Taxotere (TXT) was investigated.

Method: Using a cross over design the respective CY was applied alone at cycle I and proceeded by AMI 910 mg/m² 15 min infus at cycle II. Drug schedules consisted of EPI 120 mg/m² 30 min inf, MMC 12 mg/m² bolus, PAC 200 mg/m² 3 H inf. and TXT 100 mg/m² 1 HR inf. Different reversed phase HPLC methods were used determining CY plasma levels.

Results:

AUC ng/ml.H	n	CY	AMI/CY	p (t-test)
EPI (0–6 H)	13	895	1129	0.01
MMC (0–6 H)	15	776	758	0.44
PAC (0–24 H)	16	9780	6612	0.006
TXT (0–3 H)	11	2723	3370	0.1

Conclusion: different effects of AMI on PK of applied CY could be documented: AUC of PAC was decreased (30%) and of EPI increased (26%), latter confirming our results obtained with Doxorubicin. In contrast AUC of MMC and TXT were not significantly changed. Potential mechanisms (on protein binding, distribution, metabolism) are discussed.

1110 ORAL

Bilirubin: Baseline value and transient increase of total bilirubin (BIL) may be used as good predictor of CPT-11'S toxicity

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Total bil rise between days 3 and 6 post treatment, usually reversible by days 7–10, was seen during an ongoing CPT-11/Oxaliplatin (L-OHP) combination phase I trial (see abstract Cvitkovic et al.), the rise being both direct and unconjugated bil. After 37 cycles administered, we observed 30 cycles (81%) with transient bil increase. Amongst the 30 cy, 15 cy had baseline bil <12 μmol/L (group A) and 15 cy bil >12 μmol/L. Grade 3–4 neutropenia was seen in 2 cy (13%) of group A and 9 cy (60%) of group B (p: 0.008). The predictive power of baseline bil values (≥12 μmol/L) and the transient bil increase (x 2 the baseline value) with the observation of neutropenia/diarrhea grade 3–4 (CTC-NCI) is shown below:

	Diarrhea gr 3–4		Neutropenia gr 3–4	
	Sensitivity	Specificity	Sensitivity	Specificity
Baseline bil ≥12 μmol/L	60%	52%	78%	68%
Bil increase x 2 baseline	60%	73%	50%	80%

A retrospective review of phase II single agent data of CPT-11 at 350 mg/sqm q 3 weeks elicited 43 pts where first cy of treatment had bil levels at days 3–7 available. The mean differences between baseline and maximum bil value (μmol/L) were:

	Diarrhea	p: 0.009	Neutropenia	p: 0.18
Bil values μmol/L (mean)	G 0-1-2	G 3–4	G 0-1-2	G 3–4
Baseline	14.28	12.87	8.45	19.94
Maximum	16.01	28.75	1.74	30.46
Difference	1.72	15.87	3.30	10.53

The present observation is ongoing retrospective and prospective assessment in other CPT-11 trials with the aims of optimizing individual CPT-11 doses and its safety.