D/AD mg/m²	Pts(cy) Ent/Ev	Neutropenia G4 Pts	G4 (cy)	G4 m. dur.(range)	Mucositis Pts G1	G2	G3	Feb Neutro Pts	DLT Pts
50/40	3/3 (18)	1	(2)	3 (3–3) d	1	1	0	0	0/3
60/40	8/8 (39)	8	(36)	5 (2–10) d	6	1	0	3	2/8
60/50	8/4 (10)	4	(10)	6 (3–8) d	4	0	0	2	0/4
75/50	7/0 too early								

Except short lasting grade IV neutropenia, no grade 3–4 non hematological toxicity was observed. No CHF nor LVEF drop outside normal limits was observed. The toxicity data allow protocol continuation at dose level IV. As of March 95, there are 26 pts included (50% received prior anthracyclines). 16 pts are evaluable for response: 7 PR (5 mess. + 2 eval.), 2 CR (1 eval), 6 NC (3 still ongoing) and one PD. PK profile of D, done in all pts will be available in this ongoing study. This combination is feasible, well tolerated and seems very active in MBC.

936 POSTER

A BAYESIAN DOSING METHOD FOR CARBOPLATIN (CBDCA) IN CLINICAL PRACTICE

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The experience we have acquired with cisplatinum (CDDP) has permitted us to use a similar Bayesian dosing method for the administration of carboplatin (CBDCA): with continuous infusion of the drug during 120 hours, prior estimation of pharmacokinetic parameters and adaptation of the daily dose according to total platinum plasma concentration. Our first step was to define a reference population and to validate our method for theoretical larger plasma concentrations of 1.0, 1.5 and 1.8 mg/l. 79 patients with a median age of 56 years were treated with CBDCA for different types of cancer (head and neck, gastrointestinal, genitourinary...). Treatment protocols differed according to the type of cancer and its grade (associations with radiotherapy and/or polychemotherapy). The infusion times were 120 hours according the use of a volumetric pomp and an implanted venous access port. The measured platinum concentrations at the end of infusions were respectively 1.0 mg/l ± 0.095, 1.49 mg/l ± 0.13 and 1.8 mg/l ± 0.17, compared with the theoretical end-point (1.0, 1.5 and 1.8 mg/l). The median dosages of CBDCA were 280.0 mg/m² ± 40.0 mg/m² for a maximal theoretical concentration of 1.0 mg/l, 416.5 mg/m² ± 90.0 for 1.5 mg/l and 523.5 mg/m² ± 101.0 for 1.8 mg/l. These doses lead to a total platinum plasmatic AUC of 218.0 mg/l × h ± 61.7 for theoretical end-point of 1.0 mg/l, 293.1 mg/l × h ± 81.4 for 1.5 mg/l and 375.0 mg/l × h ± 129.3 for 1.8 mg/l. The residual concentration of total platinum varied from 0.01 mg/l to 0.57 mg/l for the alternated courses and the non-alternated courses. The Bayesian dosing method of CBDCA is perfectly applicable in clinical practice. It allows us to control the major side effects of the drug.

937 POSTER

PHASE I TRIAL OF GL331, A NOVEL TOPOISOMERASE-II (T-II) INHIBITOR FOR ADVANCED REFRACTORY CANCER

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GL331 (G) is a novel epipodophyllotoxin T-II inhibitor active in both etoposide (E)-sensitive and E-resistant cells. G's superior activity over E is due to better drug transport in both parental and resistant cells. We did a phase I study of G in patients (pts) with advanced refractory cancer to determine maximum tolerated dose (MTD) and pharmacokinetics (PK). G is given as a 2–3 hour iv infusion daily × 5 days Q 21 days, with intra-pt dose escalation as tolerated. We treated 33 pts at starting doses of 6–375 mg/m²/day × 5 days (3 pts/cohort). Median age is 58; 25 pts had PS of 1. Tumor types are non-small cell lung (NSC) (19), colon (7), head/neck (3), small cell lung (3), renal (1). 21 pts had prior XRT and 32 had prior chemo (13 with 2 regimens). Clinical activity was seen in 2 pts with NSC and 1 with colon cancer. At 375 mg/m²/day × 5 days, 2/3 pts had grade 4 neutropenia and thrombocytopenia (nadir at day 12–15) at cycle 1, thus defining MTD. Other toxicity was alopecia and nausea/vomiting. Complete toxicity and PK data will be presented.

938 POSTER

DOCETAXEL (D) IN COMBINATION WITH VINORELBINE (V) AS FIRST LINE CT IN PTS WITH MBC: PHASE I DOSE FINDING STUDY

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Both D and V were found to be active as single agent in MBC. Preclinical studies demonstrated a therapeutic synergism when the two drugs were combined simultaneously (AACR 1994). For these reasons, a phase I study of D in combination with V started on 6.94. Objectives were to determine the MTD and the recommended dose of V, 30 mn I.V., d1 and d5 followed by D over 1 hr I.V. d1 q. 3 wks to pts previously untreated with CT for MBC (Prior Adjuvant CT allowed). Premedication with 3 days steroids + Daflon 500 mg® was used from study entry. Eligible pts had meas and/or eval. disease, WHO PS ⩽ 2. To date 17 pts received 73 cy. Main toxicities were as follow:

D/V mg/m²	Ent/Ev Pts	Nb cy	Neutropenia G4 Pts (cy)	G4 m. dur. (range)	Mucositis G1	G2	G3	FN	PNS G1	Nb	Fluid retent m.cum dose mg/m²
60/20	3/3	(18)	2 (15)	8(4–12)	2/3	1/3	0	0	3/3	1/3	360
75/20	5/4	(22)	4 (21)	8(2–8)	1/4	2/4	0	0	2/2	0/4	450
75/22.5	4/4	(17)	4 (16)	7(4–8)	1/4	1/4	2/4	3/4	2/2	2/4	210
85/20	4/3	(7)	3 (7)	5(4–7)	1/3	2/3	0	1/3	NA	0/3	170

At the 3rd dose level, 2 pts developed DLT (febrile intropenia) concomitant with grade 2–3 mucositis. Less toxicity (hemato and non hemato) was observed within the 4th dose level with reduced dose of V. Activity: 6 pts with meas disease: 3 PR/3 NC, 6 pts with eval disease: 3 IMP/3 NC. *Conclusion:* the last step currently explored consists of D: 100 mg/m² and V 20 mg/m². This preliminary analysis suggests promising activity. Preliminary data indicate that the premedication used reduces the incidence and severity of FR. No symptomatic PNS was observed. Pharmacokinetic data will be reported.

939 POSTER

ELEVATIONS OF LFTS WITH GEMCITABINE ARE MILD, TRANSIENT AND RARELY RESULT IN WITHDRAWAL OR DOSE ADJUSTMENT

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Gemcitabine is a novel pyrimidine analogue with a modest toxicity profile and activity in a variety of solid tumours including NSCLC. The databases of 22 studies using a dose of 800–1250 mg/m² either W × 3, q4W or W × 7, q8W → W × 3, q4W have been integrated. WHO toxicity grades for LFTs were assigned mathematically with no regard to causality. This database consisted of 979 patients, 3,521 cycles and 10,120 injections. At entry, WHO grades ⩾1 were recorded for 32.4% of patients for alk.phos. (AP), 16.3% for AST, 12.9% for ALT & 2.7% for bilirubin (BR). 1/3 of patients had liver metastases. WHO grade 1, 2, 3 & 4 ALT elevations occurred in 30.3%, 11.3%, 2.6%, 0.5% of cycles & 36.9%, 21.2%, 7.9% & 1.7% of patients respectively. AST elevations occurred in 34.4%, 9.2%, 2.4%, 0.5% of cycles & 39.3%, 19.5%, 6.5% & 2.0% of patients respectively. AP elevations occurred in 23.3%, 10.1%, 3.2% & 0.8% of cycles & 29.7%, 17.1%, 6.6% & 1.9% of patients respectively. BR elevations occurred in 3.3%, 1.0%, 0.5% & 0.2% of cycles & 7.1%, 2.8%, 1.8% & 0.8% of patients respectively. There was no evidence of cumulative toxicity. The median distribution of maximum ALT values increased from 50% of the upper limit of normal at baseline, to 123% & 130% after 1 & 2 cycles but then decreased with subsequent cycles. Gender, age, prior therapy, dose or duration of therapy did not affect toxicity. 0.5% (5/979) of patients were withdrawn & only 0.5% (58/10,793) protocol defined injections were adjusted for hepatotoxicity. Transaminase rises occur frequently with gemcitabine but they are usually mild, non-progressive & rarely necessitate stopping treatment.