breast cancer) had a partial response of 6 weeks duration. The MTD has not been reached and the next dose escalation will be 100 mg/m$^2$. It is clear that coadministration of folic acid ameliorates the clinical toxicities seen with lometrexol.

932 POSTER

## HIGH DOSE CONTINUOUS INFUSION (CI) IFOSFAMIDE WITHOUT HEMATOPOIETIC SUPPORT IN HEAVILY PRETREATED BREAST CANCER (BC) AND SARCOMA (S) PATIENTS

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Ifosfamide (IFO) is an oxazophosphorine with a different activity and toxicity profile than cyclophosphamide. Its use together with uroprotective agents has allowed safe administration and dose-escalation. We report the results of a phase II trial of IFO at high doses in heavily pretreated BC and S patients. IFO was administered in a 168 hour-CI through a central venous access, for a total dose of 14 g/m$^2$ q3w. MESNA was administered together at equimolar doses. Ondansetron, 8 mg/8 h po was used as antiemetic treatment. No hematopoietic support was used. We included 10 BC and 14 S patients with disease progression during salvage chemotherapy at conventional doses. Mean previous lines of therapy 3 (range 1–5), 20 had received previous treatment with conventional-dose cyclophosphamide or IFO. All had received previous adriamycin. Median age 44 (range 18–62), 12 males and 12 females. Median number of cycle 3 (range 1–8) for a total of 81 cycles of therapy. Worst WHO grade toxic reaction for each patient: grade III–IV leukopenia in 65%, grade III nausea and vomiting in 40%, grade III neurotoxicity in 5%, grade II nephrotoxicity in 5%. Neurologic and renal toxicity were reversible. 9 patients were admitted for neutropenic fever, with two documented septic episodes. Treatment had to be discontinued in 2 patients after 2 cycles (1 renal toxicity, 1 gastro-intestinal-GI-toxicity). 20 patients are evaluable for response (4 did not finish the first cycle of therapy, 3 for early disease progression, 1 for unacceptable GI toxicity). Partial responses in 2/8 (25%) BC, and in 3/12 (25%) S. No complete responses were recorded. 65% had disease stabilization, and 10% had disease progression. 3 with S and 1 BC underwent further high dose chemotherapy with transplantation after assessment of chemotherapy sensitivity with high-dose IFO. Median duration of response was 5 months. Median overall survival was 6 months (range 2–11+). In conclusion, CI of IFO for 168 hours is an active regimen in highly pretreated BC and S. The addition of hematopoietic growth factors and further antiemetic agents could improve the toxicity of this regimen. Additionally, this regimen could be combined with non-myelotoxic drugs.

933 POSTER

## OXALIPLATIN (L-OHP®): GLOBAL SAFETY IN 682 PATIENTS (PTS)

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L-OHP® is a Dach platinum with significant activity in pretreated advanced colorectal cancer. In order to describe its safety profile, we gathered the individual data of 682 patients (pts) who received 4303 cycles (cy) from 9 studies (seven phase II and two phase III).

*Treatment:* L-OHP® was given as a single agent (SA, in 4 studies (40% of pts) and combined with 5-FU folinic acid (FFL) in 5 studies (60% of pts). L-OHP® was administered in 5 different schedules: 130 mg/sqm/d1 iv over 2 hrs q3 wks in 37% of pts, 130 mg/sqm/d1 iv over 6 hrs q3 wks in 5% of pts, 100–200 mg/sqm continuous infusion (CI) over 5 days q3 wks in 20% of pts and 100–200 mg/sqm chronomodulated (CM) on 5 days q3 wks in 38% of pts. *PT Characteristics:* Sex M/F: 63/37% PS (WHO) 0–1/2–3: 81/19%. Median age: 60 yrs. Tumor diagnosis: colorectal 80%, H&N 6%, melanoma 5%, other 9%. Pretreatment by chemotherapy (CT): 47%. Baseline abnormality grade (gr) 1–2: anemia 13%, WBC 3%, renal 2%, hepatic 88%, diarrhea 6%. *Methodology:* Separate univariate and multivariate analyses were performed for single agent and combination studies, influence of the following prognostic factors was sought: age, sex, PS, previous CT, modality, renal baseline status. Each toxicity was evaluated according to the overall incidence (gr 1–4), severity (gr 3–4) and baseline status. *Results (WHO and WHO modified scale):* No drug related toxic death occurred. Global results are shown in the following table.

| Toxic effects | Incidence (gr 1–4) | | Severity (gr 3–4) | | Prognostic factors |
|---|---|---|---|---|---|
| | SA | FFL | SA | FFL | |
| Hematology | 22% | 35% | 2% | 6% | Sex:F-PS:2-3*** |
| N-V* | 65% | 90% | 11% | 22% | None |
| Diarrhea | 30% | 85% | 4% | 25% | None |
| Neurologic** | 80% | 83% | 3% | 19% | Cumulative dose |

*With prophylactic antiemetic treatment. **WHO modified scale. ***Anemia.

Sensitive peripheral neuropathy is the most frequent limiting toxicity. Grade III neurotoxicity (functional impairment) appears in 12% of the pts at a median dose of 900 mg/sqm (range: 200–2525). According to Kaplan–Meier model, the risk of developing a severe neurotoxicity is: 10% after 6 cy (780 mg/sqm) and 50% after 9 cy (1170 mg/sqm). Its reversibility was evaluated after discontinuation in 78% of pts with ⩾gr 2 neuropathy. Regression of symptoms was observed in 82% of these pts (median follow-up: 3–4 months) and disappearance for 41% of them (median follow-up: 6–8 months). Hematological and digestive toxicities were acceptable and caused discontinuation of the treatment in only 3 pts. Other severe toxicities were immediate intolerance (hypotension, faintness) in 1% of pts. There was no renal or auditive toxicity episode. *Conclusion:* Oxaliplatin can be administered safely by CI, CM or 2–6 hrs infusion at 130 mg/sqm q3 wks. Its association with 5-FU/folinic acid does not enhance its toxicity as it is very well tolerated.

934 POSTER

## PACLITAXEL (P) AND EPIRUBICIN (E) IN ADVANCED BREAST (ABC) AND OVARIAN CANCER (AOC): A PHASE I STUDY

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We have started a phase I study in ABC and AOC pts to determine the maximum tolerated dose (MTD) of P to be given with E. Up to now, 21 pts (10 MBC and 11 AOC) have been accrued. Patient characteristics: median age 59 y (36–71); median PS (ECOG) 0 (0–1); all MBC pts had received adjuvant chemotherapy and all AOC pts were pretreated with cisplatin regimens; 18 pts were pretreated with a cumulative E dose of 360 mg/sqm. P was given i.v. by a 3 hrs c.i. at 135 mg/sqm (9 pts); 155 mg/sqm (6 pts); 175 mg/sqm (5 pts) and 200 mg/sqm (1 pt). E was given at a fixed dose of 90 mg/sqm i.v. bolus. Courses were repeated every 21 days. All the pts have been submitted to a clinical and instrumental cardiological monitoring including: physical examination, EKG, EKG Holter, late potentials, transoesofageal electrophysiologic study, cardiac echo-doppler. 81 courses have been administered: 46 at level 1, 26 at level 2, 12 at level 3 and 1 at level 4. The main side effects was: G4 neutropenia in 57% of the courses lasting a median of 4 days (1–6). No cardiac toxicity has been observed; the median left ejection fraction was 59% at study entry and 54% after 7 courses (total cumulative dose of E = 990 mg/mq). Response rate was 62.5% in ABC and 44.4% in AOC. PE is an active regimen; the main toxicity is short-lasting neutropenia and the MTD has not yet been reached. The study is ongoing.

935 POSTER

## A PHASE I STUDY OF THE COMBINATION OF DOCETAXEL (D) AND ADRIAMICIN (AD) IN FIRST LINE CT TREATMENT OF METASTATIC BREAST CANCER (MBC)

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The combination of D and AD is a logical attempt to optimize MBC therapy. The ongoing phase I trial has the objective to determine the DLT, MTD and RD in previously untreated pts with CT for MBC with measurable and/or eval disease receiving AD IV bolus followed by D 1 h IV infusion q3w. Prior Adjuvant CT with anthracycline (less than 300 mg/m$^2$) was allowed provided at least a ⩾12 month interval before study entry. Pts were required to have normal baseline LVEF monitored every 2 cycles. Prophylactic premedication is given with 3d. steroids (starting from d-1 8 mg every 6 hours) and Tanakan® from the day of 1st infusion. At least 3 pts are entered by dose level. The main toxicities are as follows:

| 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.