continuously assumed at the planned dose of 4 g/daily, or at the maximum tolerated dose, 3 g in 2 pts and 2 g in the others. More than 50% reduction of tumor mass (PR) was obtained in 3 pts, stable disease in 3 and progressive disease in 1. The toxicity of EAP + MIT was mild to moderate and only 2 patients experienced a grade 3 hematologic toxicity (WHO criteria). The 3 pts who had partial response survived 12, 48+, and 14 months, respectively; the pts who showed stable disease survived 8+, 9 and 24 months, respectively. The association of MIT to EAP chemotherapy scheme appears to be feasible with acceptable toxicity.

965 PUBLICATION

PLATINUM-DNA ADDUCTS IN PERIPHERAL BLOOD LEUKOCYTES OF PATIENTS RECEIVING CISPLATIN- OR CARBOPLATIN-BASED CHEMOTHERAPY. CORRELATION WITH CISPLATIN *IN VITRO* TREATMENT AND WITH CLINICAL ACTIVITY

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Platinum (Pt)-DNA adducts by means of Inductively Coupled Plasma Mass Spectroscopy (ICPMS), were determined in peripheral blood leukocytes of 46 patients treated with Cisplatin- or Carboplatin-based chemotherapy, before the beginning of chemotherapy, and at 1 h and 24 h after the end of Cisplatin (or Carboplatin) infusion on each 1st and 3rd chemotherapy cycle. In basal samples Pt-DNA adducts were never detected. In 33 patients no correlation was found between the response to chemotherapy and the Pt-DNA adducts levels. In 20 patients, Pt-DNA adducts were determined in peripheral blood leukocytes withdrawn before the beginning of chemotherapy and incubated *in vitro* with Cisplatin (15 μg/ml in RPMI medium). In these leukocytes median Pt-DNA adducts was 8.64 fmol/ug of DNA (range = 1.6–25.4). A significant correlation was found between adducts formation *in vitro* and *in vivo* at the 1 h after chemotherapy time point ($r = 0.664$; $P = 0.0113$); it was lost at the 24 h after chemotherapy time point ($r = 0.241$; $P = 0.305$). No correlation was found between *in vitro* adducts formation and response.

966 PUBLICATION

FEASIBILITY OF 5-FU THERAPEUTIC MONITORING

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5-FU therapeutic monitoring was performed, in 26 patients with localized or disseminated epidermoïd tumour of various origin, during 64 chemotherapy cycles containing 5-FU 1000 mg/m^2 in continuous infusion (J1–J5) and CDDP (100 mg/m^2 J1 or 20 mg/m^2/j J1–J5). Blood samples were collected daily (8 a.m., 4 p.m.). 5-FU HPLC analysis used the method of Christophidis. Dose reduction of 5-FU was programmed according to the method of R. Fety using the J1–J2 and the J1–J5 5-FU area under the curve (AUC). An average of 2 cycles was administered.

During the 1st cycle: J1–J2 5-FU AUC averaged 15751 μg l^{-1} h^{-1} ± 12309 (3902– 56620) confirming the great interpatient variability. In 4 patients J1–J2 5-FU AUC > 20000 μg l^{-1} h^{-1} obliged to cancel chemotherapy at J3. J1–J5 5-FU AUC averaged 46161 μg l^{-1} h^{-1} ± 20020 (18380–90200). We observed a 5-FU accumulation process, characterised by an increase of daily 5-FU AUC in 18 patients. 5-FU dose reduction was scheduled in 27 cases and necessitated a further decrease during the chemotherapy cycle in 9 cases. 5-FU monitoring allowed a reduction in the toxicity which were less frequent for the cycles with J1–J2 5-FU AUC < 20000 μg l^{-1} h^{-1} or J1–J5 5-FU AUC < 30000 μg l^{-1} h^{-1}. Fourteen objective responses were obtained with 2 complete responses. J1–J5 5-FU AUC did not differ between responders and non responders.

These time consuming techniques must find their role during more prolonged chemotherapy.

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967 PUBLICATION

CISPLATIN, VINORELBINE AND TAXOL PLUS G-CSF AS SALVAGE CHEMOTHERAPY IN PATIENTS WITH REFRACTORY SOLID TUMORS: PRELIMINARY RESULTS

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A frequent problem in clinical oncology is tumor resistance to chemotherapy. Fifty eight patients with different malignancies (breast: 9, NSCLC: 13, SCLC: 4, colorectal: 7, bladder: 3, head and neck: 5, ovarian: 2, cervical: 2, gall bladder: 1, renal: 1 and 1 unknown primary site) entered a prospective study and received CDDP 80 mg/m^2 d1, Taxol 150 mg/m^2 and Vinorelbine 20 mg/m^2 d2 in a 3-weekly schedule to evaluate the efficacy and toxicity of the regimen. All patients were supported by G-CSF (5 μg/kgr) sc/d, d5–d15. Thirty patients were men and 18 were women. Mean age of patients was 62 years. All patients had received 1st line treatment for advanced disease without response whereas 2nd and/or 3rd line treatment has failed in 16 of them. All women suffering from breast cancer were characterized as anthracycline resistant, while all patients with lung cancer were CDDP- and VP-16-resistant. Thirty two patients received more than 2 cycles of treatment and were evaluable for response. Twelve patients (38%) presented a partial response. Fourteen patients (43%) presented stabilization of disease or minor response while the remaining 6 pts (19%) had progressive disease. Among responders 3 pts had NSCLC, 1 SCLC, 5 breast cancer, 1 ovarian cancer, 1 colon cancer and 1 bladder cancer. The main toxicity of the regimen was myelosuppression and occurred between d_8–d_{17}. Most patients had sufficient recovery of blood counts to begin at time the next cycle. A granulocyte count of <1.000/μ.L occurred in 10 of 116 (9%) courses, but 3 patients required hospitalization for neutropenic fever and 1 of them died from sepsis. Other toxicities were mild. These preliminary results indicate significant efficacy of the regimen, but additional follow up period and patients are required to obtain more accurate conclusions.

968 PUBLICATION

CISPLATIN-PACLITAXEL WEEKLY ADMINISTRATION. A DOSE-FINDING STUDY

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To determine the MTDs of both paclitaxel and cisplatin when given in a weekly schedule, we have conducted this phase I study. To date, 15 patients with different neoplasms (6 lung, 4 ovarian, 5 others) have been treated, for a total of 93 courses. The starting doses of cisplatin and paclitaxel were 25 mg/m^2/week and 45 mg/m^2/week respectively. Dosage of the two drugs was alternately escalated by 5 mg for CDDP and 10 mg for paclitaxel until dose limiting toxicity occurred in one third or more patients of each cohort during the first 6 courses. At the 4th escalation (CDDP = 30 mg/m^2/week and paclitaxel 65 mg/m^2/week) 2/6 patients experienced DLT (in both cases it was neutropenia). Neurotoxicity was very frequent. It occurred in 7/15 patients and in 3 was of grade 2 WHO. Four patients complained of painful, although reversible, cramps. Mucositis and diarrhea were also frequent but mild. They occurred in 10 and 7 patients, respectively (only one patient had grade 3 for diarrhea). In conclusion, neutropenia seems to be the DLT when CDDP and paclitaxel are administered together in a weekly schedule. The MTDs are CDDP = 30 mg/m^2 and paclitaxel = 55 mg/m^2 in absence of hematopoietic growth factors. A further evaluation of the level 4 (CDDP = 30 mg/m^2 and paclitaxel = 65 mg/m^2) using G-CSF is ongoing.

969 PUBLICATION

ERYTHROCYTES AND THE DISTRIBUTION OF MITOMYCIN C (MMC)

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The E is an important component of whole blood and can act as a transporter and bioreactor. We have recently described an instrument allowing the improved separation and simultaneous analysis of E and plasma (P) fractions †.

We report a study of these fractions in 6 patients who received MMC 6 mg m^{-2} (9 to 12 mg) as an intravenous bolus for the treatment of

NSCLC. Blood was sampled regularly, and E and P separated immediately using the MESED instrument (Fabre, Kelmis, Belgium). MMC concentrations were determined using HPLC. Mean P C_0 was 591 ng/ml (SD 40) and mean P $t_{1/2}$ 50 minutes (SD 8). In most samples, MMC levels in E were less than those in P, but concentration time profiles were of a similar shape (E/P ratio 0.77 [SD 0.25]), until approx. 80 minutes after injection, when MMC was no longer detected in E, despite significant quantities in P. This may reflect loss from E, by redistribution, or transformation within E; investigation of this phenomenon is continuing.

† *Clin Biochem*; 27:195–196 (1994).

970 PUBLICATION

AN EVALUATION OF THE NEUROTOXICITY OF A PHASE I DOSE FINDING STUDY OF DOCETAXEL (D) IN COMBINATION WITH VINORELBIN (V)

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D, belonging to the taxoid class of anticancer agents, enhances microtubule assembly and inhibits the depolymerization of tubulin. The cytotoxic activity of V is through inhibition of the microtubule assembly. D and V have both shown clinical activity in advanced breast cancer as single agent. Additionally, therapeutic synergism has been observed in preclinical studies when the two drugs are combined simultaneously. Thus, a phase I study of a combination of these 2 drugs commenced in patients with metastatic breast cancer. However, as D. and V. induce mild neurotoxicity, neurological effects of this combination were evaluated. Neurological function at baseline, during (every 2 cycles and at the end of the study), and following treatment, in 13 metastatic breast cancer patients treated with docetaxel (60–85 mg/m^2) and vinorelbine (20–22.5 mg/m^2—D1–D5), none of them treated with vinca-alcaloids and/or CDDP, were prospectively evaluated. Deep tendon reflexes decrease was the most frequent abnormal finding, which occurred in 10 patients (77%). Mild, temporary and reversible grade 1 asymptomatic paresthesia were seen in 4 patients (31%). Pin sensibility, vibration sensation and muscular strength were always normal. Median and peroneal motor nerve conduction velocities, as well as median sensitive nerve conduction velocity, remained in the normal ranges. Peripheral neurotoxicity induced by the docetaxel-vinorelbine combination therapy appears to be mild (grade 1 according to NCI toxicity criteria).

971 PUBLICATION

PRELIMINARY RESULTS OF A RANDOMIZED STUDY OF 1 VS 2 910 MG/M/SQM DOSES OF AMIFOSTINE IN HIGH-RDI CYCLOPHOSPHAMIDE (CPM)-EPIRUBICIN (EDOX) IN PATIENTS WITH HIGH RISK BREAST CARCINOMA

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In an effort to reduce hematological toxicity of a dose-intensive regimen (CPM 1200 mg/m^2 & EDOX 75 mg/m^2 every 14 days) given for 6 courses in patients with metastatic, inflammatory or N + > 5, patients received in a randomized parallel design 1 dose (arm A) (910 mg/m^2) or 2 doses (arm B) 4 hours apart. This design aimed at giving the 2nd dose at the expected Cmax of phosphoramide mustard. This exploratory analysis concerns 6 pts and 30 cycles in each arm. No growth factor was allowed. Efficacy was estimated through blood-cell counts (G/l) at d14 (mean), as no recovery period was considered.

	WBC						PLT					
	C1	C2	C3	C4	C5	C6	C1	C2	C3	C4	C5	C6
A	1.2	2.1	1.5	2.4	.9	NA	293	262	384	155	154	NA
B	1.6	1.2	1.9	.8	.9	NA	327	238	222	76	300	NA

While incidence of emesis was similar, hypotension was observed in 15/30 cycles in arm B as compared to 0/30 in arm A.

This preliminary analysis does not suggest increased efficacy of 2 doses of amifostine compared to 1 in patients receiving dose intensive CPM-EDOX while amifostine induced hypotension was observed more often in patients scheduled to receive 2 protective doses.

972 PUBLICATION

PHASE I STUDY OF CYCLOPHOSPHAMIDE AND DOCETAXEL (TAXOTERE®) IN SOLID TUMORS

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Twelve patients (pts) received cyclophosphamide (CTX) as a 1 hr infusion followed by Taxotere (TXT) as a 1 hr infusion every 21 days. Dose levels were 0: CTX/TXT 600/60 mg/m^2 (6 pts), 1: CTX/TXT 600/75 mg/m^2 (3 pts), 2: CTX/TXT 700/75 mg/m^2 (3 pts). Pts were premedicated with dexamethasone 8 mg B.I.D. at day 0–4 and oral ondansetron. *Pts characteristics:* tumor types: breast 4, sarcoma 4, colon 3, melanoma 1; med age, 58 yrs (31–72); med Zubrod PS, 1 (0–2); med no. sites 3 (1–5); med no. of prior CT was 1 (0–4). *Response:* 2 PR (breast cancer), 2 SD (breast/sarcoma). *Toxicity:* To date, 9 pts received 18 evaluable courses. Med nadir granulocytes ($\times 10^3$)/d1: 0.7 (med duration 7 days). Neutropenic fever was seen in 3 pts in 3 cycles. *Other GRADE II tox (no. of pts, no. of cycles):* fatigue 4 (9), myalgias 1 (1), nausea 3 (3), diarrhea 2 (2), stomatitis 2 (2), skin (1). *Conclusion:* The results of this ongoing trial showed that the combination of CTX/TXT is well tolerated and with no unexpected toxicities.