was 54 (25–73), sex ratio 15 male/5 female, Performance status (WHO) means 1 (0–2). All pts were treated according to the schedule and were asked for a written informed consent. The main side effect is thrombopenia, probably dose-related. We observed thrombopenia grade 3–4 in 1/5 pts at 40 mg/m^2, 3/9 pts at 50 mg/m^2 and 2/4 pts at 60 mg/m^2. Three pts needed platelet transfusions. Grade 3–4 neutropenia was observed in 2/10 pts at 50 mg/m^2 and 1/4 pts at the 60 mg/m^2 dose level. No febrile neutropenia was noted. Nausea and vomiting were moderate. The 60 mg/m^2/w level was actually explored and could be the MTD. We observed a stabilisation of disease in 7 patients. One may conclude that Cystemustine can be used in a weekly schedule at a higher dose-intensity than previously reported, with tolerable toxicity.

961 POSTER

PHASE I STUDY OF DOCETAXEL AND IFOSFAMIDE IN PATIENTS WITH ADVANCED SOLID TUMORS

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The activity of docetaxel in our Phase II trial in sarcoma (Ann. Oncol 1994; 5: 539–542) prompted a phase I trial of docetaxel and ifosfamide in patients with advanced solid tumors. Docetaxel is administered as a 1-hr infusion on day 1 followed by ifosfamide as a 24-hr infusion. The doses are to be escalated from a starting dose of 60 mg/m^2 and 2.5 g/m^2 for docetaxel and ifosfamide respectively. All patients are premedicated with oral steroids, hydration and mesna. All cycles are repeated every 21 days. Dose Limiting Toxicity (DLT) is defined as $\geq$ 3/6 pts with > gr. 2 major toxicity, nadir to < 500 ANC for > 7 days or nadir to < 1000 ANC with fever > gr. 2 more than 3 days. Preliminary results are available on 6 patients.

Patients characteristics: median age, 58 yr (range 51–67); median WHO P.S., 1 (range 0–1) ; sex: 2 Male, 4 Female; Tumor type: 2 colon carcinoma, 2 mesothelioma, 1 cervix uteri, 1 leiomyosarcoma; 3 pts had prior chemotherapy for advanced disease, 1 pt had prior adjuvant chemotherapy.

Results: to date 6 patients received 11 cycles. No DLT has been observed.

Dose Level	Docetaxel	Ifosfamide	Toxicity
1	60	2.5	0/3 pts with DLT
2	75	2.5	0/3 pts with DLT

Toxicity: WBC nadirs occurred at day 7 with an average duration of neutropenia < 7 days. Only 1/11 cycles (9%) required patient's hospitalization for fever and neutropenia gr. 2 . All cycles were administered on day 22 . Extra-hematologic toxicities were mild and consisted in gr. 1 or 2 asthenia, alopecia, anorexia, myalgia, diarrhea, nausea. No acute hypersensitivity reaction and urotoxicity (hematuria) has been observed. Patients are being accrued at the next dose levels.

962 POSTER

BONE MARROW PROTECTION BY AMIFOSTINE (AMI) IN PATIENTS TREATED WITH CARBOPLATIN (CARBO): A PHASE I STUDY

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Background: The cytoprotective properties of AMI and the pharmacokinetic data of both CARBO and AMI and their respective metabolites led us to perform a phase I study with CARBO and 3 divided doses of AMI in solid tumor patients (pts).

Objectives: To determine the maximum tolerated dose (MTD) of CARBO, when combined with 3xAMI, and to determine the qualitative and quantitative toxic effects of 3xAMI.

Methods: AMI is given 15 min before, 2 hr after and 4 after the start of CARBO. Both AMI and CARBO are given iv over 15 min. Starting dose of CARBO was 400 mg/m^2 (escalation steps 25%→20%), and of AMI 910 mg/m^2. All pts needed to have normal hematologic parameters and a creatinine clearance $\geq$ 80 ml/min at the start.

Results: So far 33 pts entered the study: 19 male, 14 female, median age 55 yrs (range 36–66 yrs), median ECOG performance status 1(0–4), 21 without prior chemotherapy (CT). Nonhematologic toxicity (NHTOX) in the first 2 pts forced to dose reduction of AMI (740 mg/m^2). The MTD in pts with prior CT was CARBO-500/3xAMI-740 mg/m^2 (grade 4 WBC, ANC, platelets), but has not been reached in pts without prior CT (so far 1/4 pts showed grade 4 myelosuppression at CARBO-720/3xAMI-740 mg/m^2). With vigorous antiemetic protection CTC grade 3 or 4 nausea and vomiting did not occur. Hypotension occurred in 20 pts (36/76 cycles) and required further dose modifications of AMI in 6, but never led to complications. Other NHTOX (sneezing, flushing, dizziness (4 pts with grade 3), hypothermia, fatigue, lethargy, myalgia) were not dose-limiting. There were 2 partial responses and 1 minor response (colon 1, head and neck 2).

Conclusion: 3xAMI-740 mg/m^2 is safe and seems to protect the bone marrow.

963 POSTER

EXEMESTANE IN POSTMENOPAUSAL PATIENTS WITH ADVANCED BREAST CANCER: A DOSE-FINDING STUDY

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Exemestane (6-methylenandrosta-1.4-diene-3.17-dione) is a new type I aromarase inhibitor, which is active by the oral route. In a previous experience, we documented the drug's effectiveness in reducing serum oestrogen levels at daily doses ranging from 25 to 2.5 mg and, for this reason, we initiated this further study to determine the minimum effective dose. Exemestane was orally administered to 20 postmenopausal patients with metastatic breast cancer, at daily doses of 5, 2.5, 1 or 0.5 mg. The doses were randomly given under double-blind conditions (5 pts for each dose), and the changes in E_1, E_2, E_1S, LH, FSH, SHGB and DHEAS serum levels were evaluated on days 0, 7, 14, 28 and 56. The pts were considered evaluable providing they had received at least two months of therapy. The hormone analysis is still ongoing, but here we report the data concerning clinical efficacy and tolerability. All of the pts had received previous hormonal therapy for metastatic disease (9 pts >1 treatment) and 18 had also received chemotherapy (7 as adjuvant treatment and 11 for metastatic disease). The other characteristics of the pts were: median age 56 yrs (range 47–82); ER+/PgR+: 14 pts; DFI $\geq$ 2 yrs:15 pts. Soft tissue involvement was documented in 7 pts, bone in 12 and viscera in 14. Irrespective of the dose, 2 PR were obtained on soft tissue and liver; SD with a median duration of 6 months (range 3–14) was observed in 14 pts. Exemestane was very well tolerated, with nausea and asthenia (grade 1 WHO) being reported in 3 and 2 pts respectively. The hormonal data will be provided at the Congress.

Data management by I.T.M.O. (Italian Trials in Medical Oncology) Scientific Service.

964 PUBLICATION

ASSOCIATION OF MITOTANE TO ETOPOSIDE, ADRIAMYCIN AND CISPLATIN COMBINATION CHEMOTHERAPY IN ADVANCED ADRENOCORTICAL CARCINOMA (ACC)

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Mitotane (MIT) has been recently found to be able to reverse *in vitro* the multi drug resistance mediated by the MDR-1/P-glycoprotein, providing the rationale for its clinical use in combination with non specific cytotoxic drugs in the treatment of ACC. We report on the association of MIT to a etoposide, adriamycin and cisplatin chemotherapeutic regimen (EAP) in 7 patients (pts) with advanced/metastatic ACC. 3 of them were previously submitted to radical surgery and recurred after 29, 11, 7 months, respectively. 4 pts presented with locally advanced or metastatic disease *ab initio*, maximal debulking was pursued in 2 and primary tumor was judged as inoperable in the remaining.

Pt	Age(yr) /Sex	Surgical resection	Disease localizations	Hormone secretion	N° of courses	Tumor response	Response duration
1	45/M	A	adrenal+liver	F	5	SD	6 months
2	29/F	A	liver+adrenal	F + An	8	PR	7 months
3	18/F	RA	lung+mediastinum	F	6	PR	27 months
4	47/F	RA	liver+lung+adrenal	F+An	6	SD	3 months
5	62/F	-	liver+adrenal	An	4	SD	10 months
6	44/F	RA	lung	An	5	3 months	
7	46/F	-	adrenal	An 3 P	-		

F: cortisol; An: androgens; SD: stable disease; PR: partial response; P: progression; Horm: Hormone; secret; secretion.

All pts had clinical and/or biochemical evidence of hormone hypersecretion. A median of 5 EAP cycles was administered. Oral MIT was

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.

This work was supported by the "Ligues contre le Cancer de Bourgogne et du Jura".

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