toxicity, C was given at day 0 on cycle 1 (CF) and at day 6 on cycle 2 (FC), then the better tolerated cycle was continued. Escalation schedule initially projected for C was 200, 230, 260, 300, 350, 400, 450 and 500 mg/m^2. A death occurred at the level 1 (fatal dyspnea in a patient with a bulky mediastinal involvement), probably not related to the treatment, but we decided to reduce 5FU to 375 mg/m^2/day. Characteristics of the 16 patients entered in the study are following: median age: 57 years (range: 40–70), sex: 12 males, 4 females, PS: 0: 9, 1: 7; all patients had solid tumors refractory to previous treatment (colorectal: 12, oesophagus: 2, lung: 1, pancreas: 1).

Level	CPT-11/5FU	No. pts	No. Cycles	Diarrhea gr.III/IV	Neutropenia gr III/IV
1	200/500	2	2	1/0	1/1
2	200/375	8	34	3/1	0/0
3	230/375	6	12	0/0	3/0

5 hospitalizations (1 at level 3) occurred (2 for IV fluid administration) and alopecia was reported in 1 patient (level 3). Further escalation is warranted to determine the maximal tolerated dose. A pharmacodynamic study is underway to investigate potential interactions between C, F and SN38 according to the schedule administrations.

956 POSTER

PHARMACOKINETICS AND INTERCONVERSION OF THE CARBOXYLATE AND LACTONE FORMS OF IRINOTECAN (CPT-11) AND OF ITS METABOLITE SN-38 IN PATIENTS

L.P. Rivory[1], P. Canal[2], A. Mathieu-Boué[3], J. Robert[1]

[1] *Institut Bergonié, Université Bordeaux, Bordeaux*

[2] *Centre Claudius-Regaud, Toulouse*

[3] *Bellon Rhône-Poulenc Rorer, Neuilly, France*

We have developed an original HPLC method for the simultaneous analysis of the new camptothecin derivative irinotecan (CPT-11) and its active metabolite SN-38 in both their lactone and carboxylate forms. The use of the internal standard camptothecin lactone enables the detection of hydrolysis of the lactones in improperly stored samples and ensures that estimates of the ratio of the inactive (carboxylate) to active (lactone) forms determined from patient samples are accurate.

We have studied the pharmacokinetics of CPT-11 and SN-38 in five patients treated with 300–500 mg/m^2 of CPT-11 at various cycles of treatment and the following parameters for CPT-11 lactone were obtained: CL = 39.0 ± 9.6 L/hr/m^2; Vd_{ss} = 263 ± 102 L/m^2; $t_{1/2}\ \alpha$ = 3.1 ± 1.5 min; $t_{1/2}\ \beta$ = 1.4 ± 0.4 hr; $t_{1/2}\ \gamma$ = 9.6 ± 3.9 hr.

The apparent conversion of CPT-11 lactone to its carboxylate form *in vivo* was rapid with a mean half-life of 9.5 min and the carboxylate became the predominant form of plasma CPT-11 soon after the end of the infusion. The ratio of the AUCs of the lactone to total CPT-11 was 36.8 ± 3.5%. In contrast, SN-38 was present predominantly as the lactone at all times and with little interpatient variability (lactone/total AUC ratio = 64.0 ± 3.4%). This may partly explain the promising activity of CPT-11 as it is known that camptothecin derivatives are active against their target, topoisomerase I, only in their lactone form.

957 POSTER

BIOAVAILABILITY AND PHARMACOKINETICS OF ORAL ETOPOSIDE (VP16) IN ELDERLY PATIENTS

I. Robieux, P. Aita, R. Sorio, A. Lucenti, A. Freschi, D. Magri, A.M. Colussi, V. Vitali, S. Monfardini

Centro di Riferimento Oncologico, Aviano, Italy

Chronic oral therapy with VP16 in elderly patients (pts) is attractive for its efficacy in a variety of tumors, the ease of administration and good tolerability. The absorption and the elimination of the drug could be altered due to age-related physiological changes. We studied the pharmacokinetics (PK) and bioavailability (F) of oral VP16 in elderly pts. *Pts and Methods:* our 25 pts were divided in 2 groups older or younger than 65 years. Tumor type was carcinoma of the lung (n = 13), and other sites. PK studies after 100 mg oral VP16 and after 50 mg IV VP16 were done during the first cycle. Plasma samples were collected after 1, 2, 4, 6 and 24 hours, assayed by HPLC and fitted to a bicompartment model.

Results:

	Pts ≤ 65 (n = 8)	Pts > 65(n = 17)
F (%)	52.3 ± 20.0	54.5 ± 12.5
distribution volume (l/m^2)	10.5 ± 2.3	8.9 ± 2.9
elimination half-life(hrs)	7.5 ± 3.3	7.2 ± 2.1
systemic clearance (l/hr/m^2)	1.14 ± 0.58	0.89 ± 0.31

F and main PK parameters do not statistically differ between young and elderly patients, resulting in similar systemic exposure.

958 POSTER

A PHASE I STUDY OF AMIFOSTINE (AMI) AND ESCALATING DOSES OF TAXOL IN PATIENTS (PTS) WITH ADVANCED CANCER

L. Schuchter, R. DiPaola, R. Greenberg, S. Bird, J. Mollman, A. Recio, A. List, C. Taylor, D. Alberts

Univ Penn, Philadelphia, PA and Arizona Cancer Ctr U.S.A.

Ami protects marrow and peripheral nervous system toxicity from alkylating agents and platinum analogs. Dose-limiting toxicities (DLT) from taxol include myelosuppression, neuropathy and myalgia/arthralgia. Preclinical data show Ami protection of taxol toxicity to human bone marrow (BM) without protection of ovarian cancer *in vitro* and *in vivo*. In an ongoing Phase I trial, 30 min prior to taxol pts received 15 min iv infusion of 910 mg/m^2 amifostine. Following appropriate premeds, taxol 135–360 mg/m^2 as a 3 hr infusion was to be given to groups of 3 pts to DLT. In addition to routine evaluation, all pts undergo neuro exam & functional neurologic testing including nerve conduction studies & EMG at baseline & every 3 cycles. To date 9 pts with diverse cancers received 26 cycles of 135, 200 & 270 mg/m^2 and a cumulative taxol dose up to 1500 mg/m^2. Non-DLT transient grade 4 neutropenia was noted in 5 pts without complications. ≥grade 2 neurotoxicity was not seen in any cycle, ≥grade 3 myalgia/arthralgia was seen in 1/26 cycles. There has been minimal nausea and no vomiting; no pt had significant hypotension with Ami. Current taxol dose level is 270 mg/m^2 with escalation to 360 mg/m^2 testing Ami cytoprotection of high-dose taxol.

959 POSTER

COMPARISON OF PHARMACOKINETICS (PK) OF FREE AND LIPOSOME ENCAPSULATED DOXORUBICIN IN ADVANCED CANCER PATIENTS

J. Schüller, M. Czejka, S. Bandak, D. Borow, C. Pietrzak, I. Marei, G. Schernthaner

Hospital Rudolfstiftung, Instit. Pharma. Chemistry, Vienna, Austria

For Doxil, a doxorubicin encapsulated in Stealth liposomes, prolonged circulation time and enhanced tumor accumulation has been suggested. Purpose of this study was to compare PK of free Doxorubin (DOX) and Doxil given as 30 min infusion of 50 mg/m^2 respectively in 8 pts with metastatic cancer at a time interval of 3 weeks. Plasma samples were taken over 24 HR and prepared using solid phase extraction with methanole and sodium dihydrogen buffer, quantification was performed by means of reversed phase HPLC. For DOX, Cmax was 778 ng/ml and tmax was 0.48 HR, for Doxil only AUC could be calculated, as mean conc didn't reach steady state. DOX conc decreased from 700 at 30 min to 10 at 6 HR, whereas Doxil conc increases up to 2400 at 6 HR. AUC (ng/ml.H) of Doxil was significantly enhanced compared to free DOX, i.e. 25 fold from 462 to 11892 at 6 HR, and 67 fold from 484 to 32500 at 24 HR, both $P > 0.0001$. However, toxicity was not different, indicating that PK of Doxil is preferably due to liposome encapsulation. Whether this high and prolonged serum conc of Doxil favours an increased tumor tissue uptake is currently investigated in biopsy specimens.

960 POSTER

PHASE I TRIAL OF A NEW NITROSUREA IN A WEEKLY SCHEDULE

C. Terret[1], E. Goncalves[1], L. Da Costa[1], V. Urosevic[2], P. Chollet[3], J. Madelmont[3], J.P. Armand[1]

[1] *Institut Gustave-Roussy, 94805 Villejuif*

[2] *CSP 77230 Moussy-le-Neuf*

[3] *INSERM, CAC 63011 Clermont-Fd, France*

Cystemustine (Cys) is a new nitrosurea that has demonstrated a cytostatic activity against glioma, melanoma and renal carcinoma in previous trials (EORTC Clinical Screening Group). The dose-intensity was 30 mg/m^2/w at the recommended dose. With the aim to optimize these results, a new phase I trial was performed at IGR. From April to Dec. 1994, 27 patients (pts) with refractory cancer were treated with Cys administered as a 15 min IV bolus every week, during 4 weeks, in an escalating dose schedule from 30 mg/m^2 to 60 mg/m^2 with a pharmacokinetic study at each 1st injection. Twenty out of the 27 pts are evaluable. Tumor types are: Head & Neck 4 pts, renal 3 pts, mesothelioma 3 pts, colorectal 3 pts, ovary 2 pts and other tumor 5 pts. All pts were previously treated with chemotherapy and/or radiotherapy. Median age

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

L. Pronk, D. Shrijvers, D. Locci-Tonelli, J. Verweij, A.T. Van Oosterom

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

J.B. Vermorken[1], C.J.A. Punt[2], C.M. Eeltink[1], L. van Maanen[2], W. Oster[3], M.D. van Houten[4], W.J.F. van der Vijgh[1]
[1]*Free Univ. Hosp.*
[2]*Univ. Hosp Nijmegen*
[3]*USB Pharma*
[4]*EORTC New Drug Development Office, Amsterdam, The Netherlands*

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

N. Zilembo, C. Noberasco, A. Martinetti, L. Mariani, L. Rimassa, M. Del Vecchio, A. Laffranchi, S. Orefice, E. Galante, C. Sguotti[1], E. Bajetta
Division of Medical Oncology B, Istituto Nazionale Tumori, Via Venezian 1, 20133 Milan, Italy
[1]*Pharmacia, Milan*

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)

A. Berruti, A. Pia, M. Terzolo, C. Letizia[1], L. Dogliotti, A. Angeli
Università di Torino, Ospedale S. Luigi, Orbassano
[1]*Università "La Sapienza", Roma, Italy*

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