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