945 POSTER

PHASE I STUDY OF HIGH DOSE 5-FLUOROURACIL AND FOLINIC ACID IN WEEKLY CONTINUOUS INFUSION

J.M. Limacher, B. Duclos, J. Wihlm[1], D. Leveque[2], P. Dufour[3], F. Eichler, R. Keiling, J.P. Bergerat
Service d'Oncologie and IRCAD Hôpital Civil
[1]Laboratoire de Biochimie, Centre Régional de Lutte Centre le Cancer Paul Strauss
[2]Laboratoire de Bactériologie
[3]Service d'Onco-Hématologie, Strasbourg

5-Fluorouracile (5FU) is a major drug in the treatment of many epithelial tumours but despite more than 30 years of use the best way of its administration is not clearly defined. We present here a phase I study of a 5FU and folinic acid combination given at high doses in weekly continuous infusions.

Method: 5FU was given in a weekly 24 hr continuous infusion at doses comprised between 1.8 and 2.7 gr/sqm. 600 mg of calcium folinate were shared in a 200 mg loading dose and the rest of the dose given in a continuous infusion simultaneously to the 5FU. 42 patients suffering from neoplastic disease in which 5FU based chemotherapy was indicated entered the study.

Results: Up to 2.4 gr/sqm of 5FU the treatment was well tolerated with only minor side effects. At higher 5FU doses (2.5, 2.6 and 2.7 gr/sqm) the toxic manifestations became rapidly more important. Diarrhea, nausea/vomiting and hand-foot syndrome were the most frequent toxicities. Other toxicities have been observed: angina pectoris, transient encephalopathy and colectasia, a not previously related side-effect of 5FU.

Conclusion: The maximal tolerated dose of 5FU under such conditions is 2.4 gr/sqm. Up to this dose the treatment can be used in even heavily pretreated patients with respect of the quality of live.

946 POSTER

CGP 42446-PHASE I STUDY OF A NEW BISPHOSPHONATE IN PATIENTS WITH OSTEOLYTIC BONE METASTASES

A. Lipton, J. Berenson, H. Harvey, L. Rosen, E. Givant, M. Kowalski, J. Seaman, R. Knight
Hershey Medical Center, Hershey, PA, UCLA, Los Angeles, CA, CIBA-GEIGY, Corp. Summit, NJ, U.S.A.

CGP 42446, a third generation bisphosphonate, is two orders of magnitude more potent than Pamidronate in inhibiting 1.25 $(OH)_2$ D_3 induced release of calcium from mouse calvaria *in vitro*. Twenty-three patients with osteolytic bone metastases have been included in this Phase I trial. Patients received: 100 ug (7 pts.), 200 ug (6 pts.), 400 ug (7 pts.), or 800 ug (3 pts.) IV over 15 minutes q month. Patient entry continues and will include patients treated at 1500 and 2000 ug q month. No hematologic or biochemical toxicity has been observed. Side effects were mild (Grade I) and included eye irritation (3 pts.), nausea or fatigue (2 pts.), and flu-like symptoms, chills and vomiting (1 pt. each). Data on pyridinium crosslinks and C- and N- telopeptides will be presented. We conclude that CGP 42446 is a well tolerated new third generation bisphosphonate.

947 POSTER

CPT-11 METABOLISM IN BLOOD, BILE AND URINE IN CANCER PATIENTS

F. Lokiec, P. Canal, A. Mathieu-Boué, J.P. Armand, R. Bugat
Centre René Huguenin, Saint-Cloud, Institut Gustave-Roussy, Villejuif, Centre Claudius Régaud, Toulouse, RPR Bellon, Antony

CPT-11 (Irinotécan) is a water soluble semisynthetic derivative of camptothecin. It acts as an inhibitor of DNA topoisomerase I. Two patients were treated with CPT-11 for colorectal cancer. Both of them had a biliary catheter for extrahepatic biliary obstruction. The 1st patient received CPT-11 on a 100 mg/m^2 weekly schedule and the second was administered 350 mg/m^2 every 3 weeks. In plasma, the active identified metabolite SN-38 was mainly in the form of a glucuronide conjugate (ratio: 1 to 4 for 100 mg/m^2 and 1 to 12 for 350 mg/m^2. CPT-11 was mainly excreted in bile and urine as CPT-11. Cumulative biliary and urinary excretion of CPT-11 and its metabolites over a period of time up to 48 hours was 25% (100 mg/m^2 weekly) to 50% (350 mg/m^2 every 3 weeks). This means that CPT-11 might be excreted in other not yet identified forms.

948 POSTER

PHENOBARBITAL (PB) INFLUENCE ON IFOSFAMIDE (IF) PHARMACOKINETICS (PK) IN SARCOMA PATIENTS

F. Lokiec, J. Santoni, S. Weill, M. Tubiana-Hulin
Service de Pharmacologie, Centre René Huguenin, Saint-Cloud, France

Ten patients (pts) (3 males and 7 females) were treated with high-dose IF for osteosarcoma (2 pts) and soft tissue sarcoma (8 pts). At each course, the pts received 4 g/m^2 IF as a one hour iv infusion every day for 3 days. The courses were repeated every 4 weeks. PB treatment was only started at the second course and was continued for the following courses at a dose of 60 mg per day the 3 days of IF iv infusion. The PK were performed the 1st studies and 3rd day of each course (35 pK analyzed).

The results of the PK analysis showed a statistical difference of the pK parameters between the 1st and the 3rd day of each course without or with PB. The mean values of AUC Cl and t1/2 for the 1st and 3rd day of the course without PB were respectively 1.07 and 0.51 mg/ml × h ($P < 0.00005$) 3.74 and 9.01 l/h/m^2 ($P < 0.005$), 5.50 and 2.52 h ($P < 0.00002$).

For the following courses with PB, no difference for the PK parameter values was found among all the 1st days and among all the 3rd days of treatment. The conclusion of this study is that PB concomitant administration does not influence IF pharmacokinetics.

949 POSTER

DIFFERENTIAL EFFECTS OF IFOSFAMIDE ON LYMPHOCYTES SUBSETS CORRELATE WITH GLUTATHIONE METABOLISM AND CYSTINE UPTAKE

G. Multhoff, M. Wiesnet, C. Botzler, T. Meier, A. Allenbacher, R.D. Issels
GSF-Institut für Klinische Hämatologic and Medizinische Klinik III, Klinikum Großhadern, D-81366 München, Germany

We used human peripheral blood lymphocytes (PBL) as a model system for investigations of cytostatic drugs on human cells *in vitro*. We studied the influence of the activated alkylating agent ifosfamide (4-OH-1F) on CD3$^+$cytotoxic T lymphocytes (CTL) and CD3$^+$ natural killer (NK) cells. Exposure of the cells to 4-OH-IF reduces significantly the cytolytic activity of CTL but less effective the cytolytic activity of NK cells. This correlates with the ability of ifosfamide to decrease differentially the intracellular glutathione (GSH) levels of the two cell types. Analysis of the initial GSH levels of CTL and NK cells of a panel of HLA different blood donors shows that NK cells have significant higher levels of GSH compared to CTL (36.5 ± 7.7 vs 27.2 ± 5.8 nmol GSH/mg protein). However, this difference in initial GSH level in NK cells compared to CTL is about 1.5-fold, whereas the resistance against an 4-OH-IF treatment that leads to an equal GSH depletion in both cell types is about 4-fold. For further analysis this discrepancy we determined the relative rate of GSH synthesis in NK cells and CTL. We could show that NK cells have an about 4-fold greater capacity of GSH synthesis compared to CTL. The synthesis of GSH in lymphocytes is rate limited by the uptake of the amino acid cysteine and its disulfide form cystine. Analysis of transport systems show that NK cells take up cystine very well, but CTL lack this transport system. Cysteine can be taken up by both cell types, but under physiological conditions the extracellular concentrations of cysteine compared to cystine are quite low. However, cystine uptake in CTL can be achieved by addition of thiol compounds, e.g. 2-mercaptoethanesulfonate (mesna), to the medium of the cells. Our data suggest that the GSH levels as well as GSH synthesis of NK cells compared to CTL is related to the difference in the transport system for the amino acid cystine.

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950 POSTER

DYSPNOEA WITH GEMCITABINE IS COMMONLY SEEN, OFTEN DISEASE RELATED, TRANSIENT, AND RARELY SEVERE

R. Nelson, P. Tarassoff
Lilly Research Laboratories, Indianapolis, Indiana, U.S.A.

In clinical trials with gemcitabine dyspnoea is commonly reported. We report here a full analysis of the incidence and severity of dyspnoea. The US Integrated Safety Summary (ISS) database records all adverse events from completed studies regardless of severity. Of 979 patients, approximately 25% of patients reported some worsening of dyspnoea at some time during therapy. Drug-related dyspnoea of any severity was reported in 8% of patients. However, many of these patients had

lung cancer or pulmonary manifestations of other malignancies. Serious dyspnoea was reported in 5% of patients, and dyspnoea at rest in 1% of patients. Dyspnoea resulted in the early discontinuation from study of 0.6% of patients. The dyspnoea is generally mild and often temporally related to gemcitabine administration. It is occasionally accompanied by bronchospasm (0.6% of patients). These events usually abate spontaneously without any specific therapy. The mechanism of this dyspnoea is not clear. The Drug Experience Network (DEN) is a separate database which reports the adverse events. Of approximately 2500 patients who received gemcitabine (single agent or in combination), 300 patients (12%) reported serious pulmonary events. 183 patients (7.3%) had dyspnoea after gemcitabine administration, but only 7 patients (0.003%) experienced dyspnoea within 24 hours of drug administration with no other obvious aetiology. This dyspnoea was transient, and patients were treated symptomatically. It is concluded that dyspnoea is seen with gemcitabine but is often disease related, transient, and rarely severe.

951 POSTER

PHASE I STUDY OF BATIMASTAT (BB94) IN THE TREATMENT OF MALIGNANT PLEURAL EFFUSIONS

K. O'Byrne, V. Macaulay, M. Saunders, L. Long, F. Gleeson, T.S. Ganesan, A.L. Harris, D.C. Talbot

ICRF Clinical Oncology Unit, Churchill Hospital, Oxford, U.K.

The intrapleural administration of the matrix metallo-proteinase inhibitor, BB94, was evaluated in the treatment of 15 patients with malignant pleural effusions. Three patients were treated at each of 5 dose levels ranging from 15–135 mg/m^2. In the patients treated at the higher levels—60, 90 and 135 mg/m^2—there was a reduction in the number of pleural aspirations in the month following as compared to the month preceding BB94 therapy (0.22 +/− 0.15 v 2.33 +/-; 0.15; $P < 0.001$). Compared to pre-treatment baseline an improvement in dyspnoea score (linear analogue scale) was also seen (121 +/− 7%; $P = 0.016$). Toxicity included a transient elevation of LFTs in 1 patient and an empyema in another. Using zymography we have demonstrated gelatinase activity in the malignant pleural fluid taken prior to therapy. In conclusion intrapleural BB94 is a well tolerated treatment with early evidence of clinical activity.

952 POSTER

PHARMACOKINETICS OF REPEATED LOW-DOSES OF EXEMESTANE (1, 2.5, 5, AND 10 MG) IN POSTMENOPAUSAL HEALTHY VOLUNTEERS

S. Persiani, I. Poggesi, P. Cicioni, M. Strolin Benedetti

Department of Pharmacokinetics and Metabolism, Pharmacia, S.p.A. 20014 Nerviano (MI) Italy

Exemestane (EXE) is a new irreversible aromatase inhibitor being developed for the treatment of hormone-sensitive breast cancer. The pharmacokinetics of EXE were investigated in 32 healthy postmenopausal volunteers treated for 7 days with doses of 1, 2.5, 5, and 10 mg/day (8 volunteers/dose). Plasma samples were collected on day 5, 6, and 7 before the daily drug administration (C_{min}) and on day 7 up to 24 h after drug intake. EXE plasma levels were determined by RIA (quantitation limit 12 pg/ml). On day 7, median EXE t_{max} was 1 h; C_{max} averaged 0.83, 2.18, 7.29, and 11.04 ng/ml; AUC(0–24 h) averaged 2.30, 6.02, 15.24, and 29.98 ng·h/ml for the 1, 2.5, 5, and 10 mg doses, respectively. The analysis of C_{min} values indicated that the EXE pharmacokinetics at day 7 were at steady-state for all doses. AUC(0– 24 h) and C_{max} were compared by one-way analysis of variance after normalization to the 1 mg dose. T_{max} were compared by Kruskal Wallis test. None of the parameters evaluated differed significantly. The correlations between AUC(0–24 h), C_{max} and the EXE dose were statistically significant. In conclusion, the pharmacokinetics of EXE are dose-proportional at least up to the dose of 10 mg/day.

953 POSTER

EARLY DETERMINATION OF CISPLATIN PLASMA CONCENTRATION IS AN INDICATOR OF RENAL DYSFUNCTION

X. Pivot, B. Médecin, M.C. Etienne, G. Milano, R.J. Bensadoun, E. Tessier, J.L. Lagrange

Centre Antoine Lacassagne, Nice, France

There are few useful clinical data on pharmacokinetics and pharmacodynamics on cisplatin (CP). The purpose of this prospective study was to analyze the relationship between CP pharmacokinetics and treatment-induced renal dysfunction. Seventy cancer patients were monitored for a total of 162 cycles (24 head and neck, 33 digestive tract, 8 lung, 5 bladder, median age (62, range 42–84). CP was administered as a single short IV perfusion every 3–4 weeks (median dose 76 mg/m^2, range 16–104). Blood samples were performed at H0, H36 and H84. Free and total CP (FCP and TCP) were measured by spectrophometric atomic absorption (detection limit 5 ng/ml). Creatinine clearance were computed (cockroft method) before CP administration and between day-2 and day-10 (creat.cl.). Biological renal dysfunction (BRD) was defined as creat.cl <60 ml/min associated with more than 30% reduction as compared to initial clearance (median initial creat.cl. 75 ml/min). CP pharmacokinetics was available at H0 for 71 cycles, H36 for 137 cycles and H84 for 117 cycles. Median values of FCP at H36 and H84 were 27 ng/ml (range 0–114) and 10 ng/ml (range 0–138) respectively. 15.6% of cycles were associated to a BRD. ANOVA including the CP dose as covariate demonstrated that FCP-H36 was significant higher ($P = 0.014$) in patients who experienced BRD (mean 37 ng/ml) than in other patients (mean 25 ng/ml). Likewise, FCP-H84 was significant higher ($P = 0.014$) in patients who experienced BRD (mean 25 ng/ml) than in other patients (mean 11 ng/ml). FCP-H0 and TCP were not significant predictors of BRD.

In conclusion, CP concentration is an indicator of renal dysfunction which could be useful for selecting the patients who may benefit from an intensive therapeutic action for increasing CP elimination.

954 POSTER

CIRCADIAN VARIATION OF DIHYDROPYRIMIDINE DEHYDROGENASE (DPD), URIDINE PHOSPHORYLASE (UP), β-ALANINE (β-ALA) AND 5-FLUOROURACIL, (5-FU) DURING CONTINUOUS INFUSION (CI) FLUOROPYRIMIDINES (FP)

A.B.P. Van Kuilenburg, R.L. Poorter, G.J. Peters[1], H. Van Lenthe, A.E.M. Stroomer, A.H. Van Gennip, K. Smid[1], P. Noordhuis[1], P.J.M. Bakker, C.H.N Veenhof

Academic Medical Centre

[1] Free University Hospital, Amsterdam, The Netherlands

There is evidence for a circadian variation of the major pyrimidine catabolic enzyme DPD. We studied the relationship between plasma levels of DPD, the anabolic enzyme UP, the Uracil catabolite β-ALA and 5-FU during CI of FP.

Methods: So far 8 patients (pts) who were treated with CI of 5-FU 300–450 mg/m^2/day or FUDR (floxuridine) 0.175–0.325 mg/kg/day for 14 days every 4 weeks entered the study. Blood samples for the determination of plasma levels of DPD, UP, β-ALA and 5-FU were taken 7 times every 4 hours on day 7 and 14 of one chemotherapy course. The amount of β-ALA was quantified by HPLC separation with postcolumn o-phtaldehyde detection. DPD and UP activities were determined in purified leucocytes with radiochemical assays. 5-FU levels were measured by GC-MS.

Results: For pts analyzed up to date a circadian rhythm was observed for the activities of DPD and UP and maximal activities were observed between 12 AM and 4 PM. A profound circadian variation was also observed for the β-ALA concentrations with peak values occurring between 4 PM and 8 PM. An inverse pattern was observed for the levels of 5-FU compared to that of β-ALA.

Conclusion: We observed not only a circadian variation of the levels of DPD and 5-FU, but also for β-ALA and UP. Surprisingly DPD and UP demonstrated the same pattern.

955 POSTER

A PHASE I STUDY OF CONCOMITANT CPT-11 (C) AND 5FU (F) COMBINATION: PRELIMINARY RESULTS

O. Rixe[1], A. Benhammouda[1], C. Farabos[2], Ch. Borel[1], T. Petit[1], G. Auclerc[1], D. Coeffic[1], G. Bastian[1], F. Grossin[1], D. Paraiso[1], J.P. Grapin[1], D. Nizri[1], M. Weil[1], H. Bismuth[2], M. Mahjoubi[3], D. Khayat[1]

[1] SOMPS, Salpétrière Hospital, Paris, France

[2] Paul Brousse Hospital, Villejuif

[3] Bellon Laboratory

CPT-11, a DNA topoisomerase I inhibitor has been confirmed to demonstrate an anti-tumor effect specially against colorectal cancer (CRC). In order to define the best schedule combining the most two active agents in CRC, we initiated in June 94 a phase I study at the starting dose (level 1) of C 200 mg/m^2 (over 30 minutes) and F (500 mg/m^2 on day 1 to 5 by IV *bolus* administration). To find a sequence-dependent