945 POSTER

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

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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

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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

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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

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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

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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

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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