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

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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

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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

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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)

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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

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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