Patients and Method: Within a Phase I-trial of the Arbeitsgemeinschaft Internistische Onkologie (AIO) the drug is currently tested for DLT and MTD. At present 17 patients have been treated up to a dose level of 60 mg/m^2 MTX-HSA once weekly up to 8 weeks.

Results: DLT has occurred, mainly stomatitis (CTC-Grade 2 or 3), beginning at the dose-level of 50 mg/m^2 once weekly. Monitoring of plasma MTX-HSA levels (modified EMIT, Syva Co., Paolo Alto, CA 94303) shows accumulation of the drug at a weekly application schedule. The terminal half-life of the drug is 15–19 days, AUC > 5000 μmol/l × h are achieved without toxicity. Tumor-response was seen in three patients: PR in one patient with renal cell carcinoma, MR in two patients with mesothelioma and renal cell carcinoma.

Conclusion: The MTD is not yet defined. The study will be continued with a bi-weekly application schedule.

1130 POSTER

Evidence for enhanced toxicity to CPT-11 in patients with Gilbert's syndrome: Two case reports

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CPT-11 acts as a prodrug in vivo, being converted to SN-38 by carboxylestearases. The topoisomerase I inhibition (antitumor activity) as the limiting toxicities are determined by free SN-38 concentration. Since glucuronidation represents the major detoxification pathway of SN-38, patients with a deficit in this enzyme's activity should have greater toxicity. We report here two cases of unexpected toxicity observed during an ongoing Phase I of the combination CPT-11/Oxaliplatin (L-OHP), where known glucuronidation deficiency was correlated with enhanced toxicity.

Patients and Methods: Patient A (a 49 year-old woman) and patient B (a 63 year-old woman), both with metastatic colon cancer progressed under previous fluoropyrimidine-based schedules. They had both been previously diagnosed as having Gilbert's syndrome and had no evidence of hemolysis.

After the first cycle of CPT-11/L-OHP was administered, they showed an increase of bilirubin (bil) in plasma (A: mainly unconjugated bil; B: conjugated and unconjugated bil). The bil increase began on days 2–3, maximal value on days 5–7, decreasing on days 9–13. The doses were A: 85/150 mg/sqm and B: 110/200 mg/sqm for L-OHP/CPT-11 respectively. Simultaneously to that reversible pattern of bil, patients A and B exhibited severe diarrhea and/or neutropenia in all of 12 cycles given (see table).

Pt/Cy	Baseline bil μmol/L (mean)	Max. bil μmol/L (mean)	Dose (mg/sqm) L-OHP/CPT-11	Limiting toxicities (grade 4)	AUC ng/ml/h CPT11/SN38/SN38G	Biliary index
A/10	27	60	85/150	diarrhea/ neutropenia	15386/419/784	8222
B/2	21	43	110/200	diarrhea/ neutropenia	29975/674/2843	7106

Conclusion: Pharmacogenetic differences in drug metabolism contribute to treatment related toxicities Low SN-38 glucuronidation should account for the enhanced toxicity evidenced by two patients with Gilbert's syndrome.

1131 POSTER

Phase I Study of paclitaxel (P) combined with 14-day topotecan (T) Continuous IV (CIV) infusion in previously treated and untreated patients (PTS)

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Purpose: 21-day CIV with T appears to have at least equal activity to the daily × 5 schedule with considerably less myelosuppression. This toxicity (tox) profile for combination therapy prompted a Phase I study to combine P 3-hr infusion q 21 days with 14-day T CIV. Preliminary results were previously reported (Proc ASCO, 1995).

Methods: Pts met typical Phase I criteria. P was given as a 3 -hr infusion followed by T as a 14-day infusion using an ambulatory CADD pump. Cassettes were changed weekly.

Results: The initial cohort consisted of 11 pts (8 F, 3 M) with adequate organ function, median PS 1, median age 63 y, and median of 2 prior chemo regimens. Initial dose level was P 135 mg/m^2 with T 0.3 mg/m^2/d × 14 d CIV. One of pts at this level had a maximum of gr 3 ANC tox and dose was escalated to P 135 and T 0.4, which gave 6/6 pts gr 3 WBC, 2/6 pts gr 3 ANC tox (no plt tox), without clinical sequlae. The study was revised to include pts without prior chemo and a new definition of MTD requiring gr 4 ANC > 5 d or neutropenic fevers/sepsis. At the same time doses were escalated to P 150 and T 0.4. 1/4 pts developed gr 3 ANC tox. At the current dose level of P 175 and T 0.4, 1 pt had no heme tox. Non-heme tox included: N/V gr 1 = 9 pts, gr 2 = 1 pt; diarrhea gr 1 = 4 pts, gr 2 = 2 pts; myalgias gr 1 = 6 pts, gr 2 = 3 pts; neuropathy gr 1 = 1 pt, gr 2 = 2 pts, gr 3 = 1 pt; fever gr 2 = 6 pts. In the initial cohort, 1 CR + 1 PR (ovarian CA) + 3 SD/11. The CR pt remained in remission 1 y before relapse and a second CR. In the second cohort, 1 PR (NSCLC) + 1 SD/5. Accrual is ongoing at the 175/0.4 level to determine MTD with full results to be presented.

Conclusion: This regimen appears to allow a well-tolerated means of maintaining both P and T dose intensity and should be tested in the Phase II setting. (Supported by CA16087, R01 CA56129 with thanks to CTEP NCI. Also supported by SmithKline Beecham.)

1132 PUBLICATION

Hormonal effects of MPV-2213ad, a novel, competitive aromatase inhibitor in healthy male volunteers. A phase I study

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Aim: The purpose of this open, dose-escalation study was to investigate the hormonal effects, safety and tolerability of MPV-2213ad, a new selective aromatase enzyme inhibitor.

Methods: Thirty nine healthy male volunteers were entered into the study. MPV-2213ad was given as single oral doses of 0.003, 0.03, 0.3, 3, 9, 30, 100 mg to three subjects at each dose level, ten subjects received 300 mg and eight subjects the 600 mg dose. Blood specimens for hematological, biochemical and endocrine analysis were taken frequently during the first 24 h and 2, 4, 7, 14 and 21 days after drug administration.

Results: MPV-2213ad induced a dose-dependent decrease in serum estradiol levels. The maximal reduction of serum estradiol levels was 83% after the 300 mg dose, the highest dose did not give additional decrease. After doses between 0.3 and 30 mg the estradiol suppression was 58–65%. The suppression lasted longer with higher doses of MPV-2213ad, a return to baseline levels was observed within 4 days after all doses. Significant increases in the serum concentrations of testosterone, androstenedione, 17-OH-progesterone, LH and FSH were observed. There were no signs of adreno-cortical suppression. The drug was well-tolerated. The adverse effects were mild or moderate and consisted of hot flushes, mild vertigo, nausea and gastro-intestinal discomfort.

Conclusion: This phase I study introduces a new competitive aromatase inhibitor. The results indicate that MPV-2213ad is a selective and well-tolerated compound with a significantly suppressive effect on serum estradiol.

1133 PUBLICATION

Phase IB study of methoxymorpholinodoxorubicin (PNU 152243; FCE 23762) administered in a 3 or 4 weekly schedule

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The lipophilic anthracycline, FCE 23762, has been shown to possess broad spectrum antitumour activity, including efficacy against multidrug resistant tumours. It appears to be activated in vivo, with resulting potency 80-fold greater than doxorubicin. The initial phase I study defined the MTD as 1.5 mg/m^2/3 weeks, but heavily pretreated patients experienced more myelosuppression at the recommended dose of 1.25 mg/m^2 than did previously untreated patients. We have studied the feasibility of administering 1.25 mg/m^2 (bolus IV) either 3 or 4 weekly in untreated cancer patients.

15 patients were entered on the 3 weekly schedule (5 renal, 3 non small cell lung cancer [NSCLC], 5 colorectal, 1 head and neck, 1 unknown origin). A further 9 patients were entered on the 4 weekly schedule (1 renal, 3 NSCLC, 3 colorectal, 2 unknown origin). Toxicity by CTC indicated no cardiotoxity; 3 weekly treatment was associated with transient grade II/III hepatic transaminitis in 10% and grade III/IV nausea/vomiting in 12% of cycles, but was absent in the 4 weekly schedule. Grade III neutropenia and