1125 POSTER

Phase I/II study of the addition of tirapazamine (TIRA) to cisplatine (CDDP)/navelbine (NVB) in patients with inoperable non small cell lung cancer (NSCLC)

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TIRAPAZAMINE (SR 259075) is a benzotriazine compound exhibiting highly selective cytotoxicity for hypoxic cells-under hypoxic condition. TIRA is bio-reduced to a cytotoxic free radical which causes DNA strand cleavage.

Synergism with CDDP has been demonstrated in vitro and confirmed in Phase I and II trials, with approximately 30% response rate in NSCLC. Pre-clinical studies suggest an additive effect of NVB with TIRA/CDDP.

We are conducting a phase I/II Study of TIRA/CDDP/NVB in chemotherapy naïve patients with measurable Stage III B or IV NSCLC. TIRA is given as an IV infusion over 120 mn followed 1 hour later by CDDP IV over 60 mn repeated every 28 days and NVB IV over 10 mn weekly. All patients receive prophylactic antiemetics.

To date, 11 patients (10 M:1 F; mean age 57 (33–4); PS 0, 1) have received at least one cycle and grading of maximal toxicity is presented in the table below for the first cycle.

Level n	TIRA-CDDP-NVB Dose mg/m²	N/V	Cr	R	Dh	O	N	FN	An	T	Ast	Co	M
		Modified NCI Toxicity scale – max toxicity											
I – n = 3	260 – 75 – 25	1	3	–	–	–	4	–	2	–	2	–	–
II – n = 3	260 – 100 – 25	2	2	1	–	–	3	–	2	–	–	–	–
III – n = 3	330 – 100 – 25	2	1	1	–	–	4	–	1	–	–	–	–
IV – n = 2	390 – 100 – 25	1	3	1	–	2	2	–	1	3	–	–	–

N/V: nausea/vomiting – Cr: cramping – R: rash – Dh: diarrhea – O: ototoxicity N: neutropenia – FN: febrile neutropenia – An: anemia – T: thrombopenia Ast: asthenia – Co: constipation – M: mucositis

Main toxicities are neutropenia (75% Grade 3/4), controlled nausea/vomiting and moderate reversible cramping (>70%). One patient experienced a grade 2 reversible ototoxicity. One death was not clearly documented but the patient was concurrently treated for a deep thrombosis and a pulmonary thromboembolism is suspected. Preliminary results indicate 4 PR, 3 SD and 1 PD out of the 8 evaluable patients. As MTD has not been reached yet, the trial is ongoing.

1126 POSTER

Phase I trial of irinotecan (CPT-11) I in childhood solid tumours

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Because of preclinical activity in neuroblastoma and meduloblastroma of the Topo 1 inhibitor CPT-11, a phase I study in children with solid tumours was initiated. The starting dose of CPT-11 (administered every 3 weeks as 120 mn infusion) was 200 mg/m² with a dose with a dose escalation of 20%.

To date, 11 patients (pts.) have been included in the first 4 dose levels. Pts characteristics are: median age 7.5 years (10 months–16 yrs), sex ratio m/f: 9/2, PS (Lansky scale): 80% (60–100), median number of previous CT lines: 3 (0–5), tumour types: 3 ependymomas, 1 astrocytoma, 1 glioma, 2 sacromas, 2 hepatoblastomas, 1 Burkitt lymphoma, 1 cavum epidermoid. All 11 pts are evaluable for the primary end point: dose-limiting toxicity (DLT) determined at the first cycle.

Dose mg/m² (n)	200 (3)			240 (3)			300 (3)			350 (2)		
NCI/CTC grade	0–2	3	4	0–2	3	4	0–2	3	4	0–2	3	4
Cholinergic syndr.	3	0	0	3	0	0	3	0	0	2	0	0
Neutrophil count	2	1	0	3	0	0	2	1	0	1	1	0
Delayed diarrhoea	3	0	0	3	0	0	3	0	0	2	0	0

In 34 cycles administered, no dose limiting or cumulative toxicity was observed. Among the 11 evaluable pts, 1 minor response (glioma) and 4 stable diseases were noted. Pharmacokinetic evaluation is ongoing.

Conclusion: DLT is not yet reached at the dose of 300 mg/m². Final results will be presented.

1127 POSTER

A randomised, double blind, parallel- group trial to evaluate the effect of the aromatase inhibitor anastrozole on the pharmacokinetics of tamoxifen (TAM) in postmenopausal breast cancer patients

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Purpose: Arimidex™ (anastrozole) is under study in combination with tam as adjuvant therapy of breast cancer. It is therefore important to (i) assess the effect of anastrozole on the pharmacokinetics of tam, and (ii) assess the safety and tolerability of combination anastrozole and tam therapy.

Methods: 34 postmenopausal women with early breast cancer, who were receiving tam (20 mg daily) as adjuvant therapy, were randomised to also receive anastrozole (16 patients) or placebo (18 patients), at 3 centres in the UK. Randomised therapy was taken for 28 days from Day 0. Blood samples were taken from each patient at days −7, 0, 14, 28 and 42, and adverse events collected from Day 0 onwards. Oestradiol and trough tam levels were measured in all samples and trough anastrozole levels in samples taken from Day 0 onwards.

Results: There was no evidence of anastrozole having any significant effect ($p = 0.92$) on the blood levels of tam. In patients receiving the combination of anastrozole and tam, oestradiol was suppressed to the level of detection of the assay (3 pmol/l), whilst in patients from the placebo group oestradiol levels were unaffected from baseline. Overall the adverse event profiles of the two groups were similar.

Conclusion: Blood tam levels were unaffected by anastrozole, and oestradiol suppression by anastrozole occurs in the presence of tam.

1128 POSTER

High dose methotrexate (HDMTX) pharmacokinetic profile in osteosarcoma patients

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Treatment results in high grade O.S. have improved increasing the doses of C.T. and a dose relationship both for responses and survival have been demonstrated for MTX peak serum levels at the end of the infusion. Concentrations above 700 μmol/L discriminate between good and poor responder pts. In a selected number of pts, we did a complete pharmacokinetic profile of MTX. The drug was administered at the dose of 12 g/sqm in a 6 hours infusions. Leucovorin was administered every 6 hours for 12 times beginning 24 hours after the start of MTX. Serum MTX measurements were taken from a venous access at time 0, 6th (end of infusion), 12th, 24th, 48th and 72nd. MTX levels were determined using MTX II Tdx System Operation (Abbott). Pharmacokinetics data were elaborated by PKS programme (Abbott) on a bicompartimental analysis. 35 infusions were evalueted about 9 patients. Mean MTX total dose was 19.82 ± 0.83 g; mean concentration level at 6th hour (C_{max}) was 961.97 ± 199.35 μmol/L, at 12th hour 252.29 ± 101, at 24th hour 16.48 ± 14.52, at 48th hour 0.38 ± 0.43, at 72nd hour 0.21 ± 0.25. Volume of distribution (Vd) was 0.334 ± 0.063 L/kg, total body clearances 0.085 ± 0.017 L/h/kg, half-time (t 1/2) 2.67 ± 0.52 h, AUC 5067.69 ± 1533.5 μmol/L/h. None of this parameters was strictly correlated with clinical response, excepted for C_{max} at 6th hour, as published before. Similarly, no correlation was found between pharmacokinetic results and toxicity excepted for concentration at 24th, 48th and 72nd hours.

1129 POSTER

Phase I-trial of a methotrexate – Albumin conjugate (MTX-HSA) in cancer patients

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Purpose: Improved pharmacokinetic properties are a major advantage of Methotrexate covalently bound to human serum albumin (MTX-HSA) over conventional Methotrexate (MTX). The halflife of MTX-HSA is compareable to native human serum albumin (19 days). Preclinical data has shown a manifold uptake of MTX-HSA in solid tumors compared to unbound MTX.

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