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)

M. Gatineau[1], O. Rixe[1], A. Rey[2], L. Trandafir[2], T. Le Chevalier[1]. [1]IGR Villejuif; [2]Sanofi Recherche, France

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

F. Pein[1], F. Doz[2], D. Frappaz[3], E. Lucchi[1], S. Moretti[2], D. Santos[1], D. Mignard[4], G. Vassal[1]. [1]IGR, Villejuif; [2]Inst. Curie, Paris; [3]Léon Berard, Lyon; [4]RPR France, Montrouge, France

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

J.S. Tobias[1], M. Baum[1], G.M. Blackman[1], M. Dowsett[2], N. King[2], A. Howell[3], H. Welch[2]. [1]Middlesex Hospital London; [2]Royal Marsden Hospital London; [3]Christie Hospital Manchester, UK

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

A. Comandone[1], A. Boglione[1], G. Bacci[3], C. Oliva[1], P. Bergnolo[1], L. Leone[2], S. Ferrari[3], C. Bumma[1]. [1]Division of Medical Oncology, S. Giovanni Antica Sede Hospital, Torino; [3]Istituto Ortopedico Rizzoli, Bologna; [2]Ospedale Infantile Regina Margherita, Torino, Italy

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

G. Hartung[1], G. Stehle[2,3], H. Sinn[3], H.H. Schrenk[3], S. Heeger[1], M. Kränzle[1], H.H. Fiebig[4], W. Maier-Borst[3], D.L. Heene[2], W. Queißer[1]. [1]III. Dept. of Medicine, Klinikum Mannheim, University Heidelberg; [2]I. Dept. of Medicine, Klinikum Mannheim, University Heidelberg; [3]FS 05, DKFZ, Heidelberg; [4]Klinik f. Tumorbiologie, Freiburg, Germany

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.