

189228: Deflexifol (a novel formulation of 5FU): Pharmacokinetics in a Phase 1 Trial in Comparison to 5FU

Stephen P. Ackland^{1,2}, Madhu B. Garg^{1,2}, Marie Ranson^{3,7}, Rebecca Jokela⁴, Daniel Brungs⁵, Morteza Aghmesheh⁶, Ali Tafreshi⁶, David Ranson⁷, Suzanne Parker⁴, Paul De Souza⁸ and Philip Clingan^{3,4,7}

¹ University Of Newcastle, Callaghan, NSW Australia ² Calvary Mater Newcastle, Waratah; HCRA and Hunter Medical Research Institute (HMRI), Newcastle, Australia ³ Illawarra Health and Medical Research Institute, Wollongong/ University Of Wollongong, NSW Australia ⁴ Southern Medical Day Care Centre Wollongong Australia ⁵ St George Hospital, NSW Australia ⁶ Wollongong Hospital, NSW Australia ⁷ FivePhusion Pty Ltd, Austimmer, NSW Australia ⁸ Ingham institute for Applied Medical Research, Liverpool, NSW Australia
Email: stephen.ackland@newcastle.edu.au

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INTRODUCTION

- Simultaneous administration of 5-fluorouracil (5FU) and leucovorin (LV) is generally not feasible.
- 5FU and LV are chemically incompatible (CaPO₄ crystals), resulting in common adverse events such as phlebitis, catheter blockage and sepsis.
- Sequential administration of 5-FU and LV increases nursing time and complications and potentially decreases efficacy.
- Collectively, these adverse events lead to poor patient outcomes due to treatment interruption and discontinuation.
- Sequential administration also does not maximise opportunity for Thymidylate Synthase (TS) inhibition by ternary complex FdUMP-MTHF-TS. So the maximum possible interaction for benefit is not achieved.
- Deflexifol, an all in one formulation of 5FU/LV with cyclodextrin (HP-β-CD 100mg/ml, 5-FU 15mg/ml & LV 1mg/ml) at pH 7, was developed to overcome this problem (Locke JM et al, Anticancer Drugs 2009).
- Preclinical testing demonstrated that Deflexifol is stable, bioequivalent to 5FU, and has reduced side effects (Stutchbury TK Anticancer Drugs 2011).

METHODS

An open label standard (3+3) phase 1 dose-escalation study (see abstract #188458, poster #2529) in 2 schedules -- 46-h infusion Q2W, or bolus weekly x6

Primary Objectives:

- Safety, tolerability, MTD (maximum tolerated dose) and RP2D (recommended phase 2 dose).

Secondary Objectives:

- PK profiles compared to historical 5FU alone; response rate (RECIST 1.1 criteria)

Limited Sampling PK of 5FU and DihydroFU:

- PK (5FU AUC, clearance [CLR] and t_{1/2} as per Ackland et al, Anal Biochem 1997) evaluated with dose 1 and 6, at 5 dose levels, compared to previous reports (Van Groeningen et al Cancer Res, 1988; Hillcoat et al Br J Cancer 1978)
 - Infusion: 1200, 1800, 2400, 3000 and 3600mg/m²,
 - Bolus: 375, 425, 475, 525 and 575 mg/m².
 - Sample times were infusion: 0, 2, 46h; bolus: 0, 0.2, 0.4, 1, 24h.

RESULTS

- 40 patients (21 infusion, 19 bolus; median age 67; 19 M, 21 F).
- PK estimates made for 34/40 patients treated with dose 1, and 24/32 patients treated with dose 6
- MTD(bolus) = 575 mg/m²:
 - No grade 3 toxicity till dose level 4 (525 mg/m²)
 - Dose level 5 (575 mg/m²) - grade 3 diarrhea 2/3 patients, neutropenia 2/3 patients
- no DLT in infusion schedule to 3600 mg/m².
- PK showed substantial inter-patient variability – CLR(bolus) 21-900 L/h, t_{1/2} 0.11-0.52 h, with intra-patient dose 6 CLR = 54-117% dose 1, and a trend to increased AUC (mg/L.h) with dose (see Tables).
- Infusion CLR and AUC estimates were highly variable (CLR range 2-1200 L/h), with many cases insufficient data.
- Compared to historical data with 5FU alone, AUC was likely well below MTD until 525mg/m² bolus and for many patients with infusion < 3000mg/m².

CONCLUSIONS

- 5FU PK with Deflexifol is similar to 5FU alone
- In each schedule AUC data supports the clinical impression of reduced toxicity at the same dose of 5FU
- Trend to increased AUC with dose - no evidence of saturation of clearance mechanisms
- Accurate estimation of infusion PK requires more than 2 time points.
- PK of Deflexifol in a phase II study is planned

RESULTS (contd.)

Pharmacokinetic Parameters (mean ± SEM)

Infusion	Dose 1			Dose 6		
	N	AUC (mg.hr/L)	CLR (L/hr)	N	AUC (mg.hr/L)	CLR (L/hr)
1 (1200 mg/m ²)	3	460.6 ± 370.1	45.5 ± 31.8	2	1490 ± 453.3	4.41 ± 3.63
2 (1800 mg/m ²)	3	1074.7 ± 305.7	3.2 ± 1.0	0	-	-
3 (2400 mg/m ²)	5	463.3 ± 90.9	75.5 ± 59.4	5	256.7 ± 149.7	64.9 ± 29.41
4 (3000 mg/m ²)	2	618.4 ± 535.0	42.31 ± 36.9	3	53.0 ± 24.7	572.9 ± 596.4
5 (3600 mg/m ²)	3	11.9 ± 4.0	706.2 ± 277.3	0	-	-
All	16	512.2 ± 134.8	170.4 ± 81.9	10	442.2 ± 259.9	205.2 ± 151.4

Bolus	Dose 1				Dose 6			
	N	AUC (mg.hr/L)	CLR (L/hr)	t _{1/2} (hr)	N	AUC (mg.hr/L)	CLR (L/hr)	t _{1/2} (hr)
1 (375 mg/m ²)	3	6.51 ± 1.11	97.1 ± 11.19		3	7.68 ± 1.21	84.66±16.67	
2 (425 mg/m ²)	3	5.54 ± 2.01	188.0 ± 76.8		3	12.37 ± 2.51	67.97±19.44	
3 (475 mg/m ²)	3	7.12 ± 3.75	201.8 ± 101.4		3	7.54 ± 2.47	129.8 ± 42.2	
4 (525 mg/m ²)	5	17.71 ± 8.19	148.4 ± 85.0		3	8.51 ± 3.77	378.3 ± 306.9	
5 (575 mg/m ²)	4	18.43 ± 3.69	59.4 ± 9.9		2	26.47± 8.09	37.8 ± 9.6	
All	18	12.21 ± 2.70	135.6 ± 31.0	0.21 ± 0.02	14	11.52 ± 2.18	147.0 ± 66.1	0.22 ± 0.02

