188458:Deflexifol (a novel formulation of 5FU) Phase 1 Dose Escalation Study of Infusional or Bolus Schedules After Failure of Standard Treatment

Philip R Clingan,[1] Marie Ranson,[3] Paul De Souza,[4] Ali Tafreshi,[5] Morteza Aghmesheh,[5] Daniel Brungs,[3] Madhu Bala Garg,[6] Suzanne Parker,[1] Rebecca Jokela,[1] Anne Henderson,[1] Stephen P. Ackland[2]

1.Southern Medical Day Care Centre, Wollongong, Australia 2. Calvary Mater Hospital, Newcastle Australia, 3. Illawarra Health and Medical Research Institute, School of Biological Sciences University of Wollongong, Wollongong, Australia. 4. University of Western Sydney, Sydney Australia, 5. Illawarra Cancer Care Centre, Wollongong Australia, 6. Calvary Mater Hospital/ Hunter Medical Research Institute, Newcastle, Australia.

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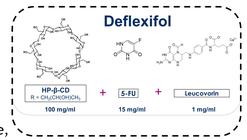
BACKGROUND

5-fluorouracil (5FU) is a commonly used anticancer agent first synthesized in 1957, and is now most commonly used with Leucovorin (LV), which enhances its clinical activity.

Sequential administration of 5-FU and LV may lead to increased nursing time, complications and potentially decreased efficacy.

Additionally, sequential administration does not maximize the opportunity for Thymidylate synthase (TS) inhibition by ternary complex (FdUMP-MTHF-TS) of 5FU metabolite, LV and TS.

Simultaneous administration is not feasible due to 5FU and LV being chemically incompatible, 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 physiological pH, was developed to improve efficacy and tolerance.

OBJECTIVES

Primary Objectives

- Determine safety and tolerability in patients with relapsed or refractory malignancy
- Determine the maximum tolerated dose (MTD) of **Deflexifol** by continuous intravenous infusion and by bolus

Secondary Objectives

- Assess Response Rate (RR per RESCIST 1.1) in subjects with relapsed refractory malignancy
- Determine the Pharmacokinetic profile of **Deflexifol**
- Determine progression free survival

METHODOLOGY

- Standard Phase 1 dose escalation trial
- Two schedules
- No intrapatient dose escalation

Bolus schedule:
Similar to Roswell Park regimen, given weekly for 6 weeks with a 2 week break. Patients enrolled in escalating dose cohorts.

Dose Level	Infusional Dose of Deflexifol
1	1200mg /m^2/46hours q2wx6
2	1800mg /m^2/46hours q2wx6
3	2400mg /m^2/46hours q2wx6
4	3000mg/ m^2/46hours q2wx6
5	3600mg /m^2/46hours q2wx6

Infusion schedule:
Similar to De Gramont regimen. Continuous Infusion over 46 hours given every 2 weeks for 6 doses.

Dose Level	Bolus Dose of Deflexifol
1	375mg/m^{2}qwx6
2	425mg/m^{2}qwx6
3	475mg/m^{2}qwx6
4	525mg/m^{2}qwx6
5	575mg/m^{2}qwx6

Inclusion Criteria

- Locally or advanced disease measurable or evaluable by RECIST 1.1 criteria
- Failed all standard treatments including 5FU
- ECOG performance of 0-2
- Life Expectancy of 12 + weeks
- Informed Consent

Exclusion Criteria

- No prior suggested DPD deficiency
- Brain metastases (untreated)
- Allergic reactions
- Concurrent treatment

Maximum Tolerated Dose (MTD):

- MTD is defined as 2 out of 6 patients experience DLTs this dose level is declared DLT dose
- The previous dose level expanded to x6 patients to confirm (MTD)

Dose-limiting toxicity (DLT) is defined as:

- Any Grade 3 or 4 non-haemotologic toxicity (CTCAE criteria)
- Grade 3 or 4 diarrhoea, failing maximal anti-diarrheal medications
- Febrile neutropenia, Grade 4 neutropenia > 7 days,
- Grade 4 thrombocytopenia > 7 days Any grade of thrombocytopenia associated with bleeding

Study Assessments:

- Safety evaluated by monitoring AEs, vital signs, hematology parameters, clinical chemistry and physical examinations
- Pre-study assessments including: Informed consent, demographics, medical history, concurrent meds, physical exam, vital signs, performance status, (standard of care) complete blood count with differential platelets and serum chemistry
- PK collection at dose 1 and dose 6,(Bolus 6 samples (0,10,20,60,120min,24hr and infusion 3 samples 0, 2 hr and 46 hr) at each of 5 dose levels, tumor markers at dose 1 and 6

RESULTS

- 40 patients
- 21 infusional,19 bolus received a total 293 doses of treatment
- No > grade 1 toxicity was noted at 375-475 mg/m^2 bolus, or at 1200-2400 mg/m^2 infusion
- The DLT in bolus schedule was grade 3 diarrhoea and myelosuppression at 575 mg/m^2
- No DLT in the infusion schedule at the maximum dose 3600 mg/m^2

Characteristic	Bolus Regimen n=19 (%)	Infusion Regimen n=21 (%)
Sex		
Male	7 (36)	12 (58)
Female	12 (63)	9 (42)
Primary Tumour Location		
Breast	5 (26)	2 (10)
Colorectal	7 (37)	17 (80)
Other Gastrointestinal	4 (21)	2 (10)
Lung	3 (16)	0 (0)
Age		
Median (range)	64 (28 – 81)	67 (37 – 78)
Prior 5-FU Treatment		
Yes	12 (63)	20 (95)
No	7 (36)	1 (5)
Lines of Previous Treatment		
≤5	13 (68)	17 (80)
>5	6 (32)	4 (20)

PRIMARY OBJECTIVE: SAFETY AND TOLERABILITY: ADVERSE EVENTS

TREATMENT RELATED GRADE III /IV ADVERSE EVENTS BOLUS

BOLUS TOXICITY		Dose Level 1 n=3	2 n=3	3 n=3	4 n=6	5 n=3
Venous Thrombosis	G3	-	-	1	-	-
	G4	-	-	-	-	-
Febrile Neutropenia	G3	-	-	-	1	-
	G4	-	-	-	-	-
Pancytopenia	G3	-	-	-	-	1
	G4	-	-	-	-	-
Diarrhoea	G3	-	-	-	-	3

TREATMENT RELATED GRADE III /IV ADVERSE EVENTS INFUSION

INFUSION TOXICITY		Dose Level 1 n=3	2 n=3	3 n=6	4 n=6	5 n=3
Raised LFTs	G3	-	1	-	-	-
	G4	-	-	-	-	-
Nausea and Vomiting	G3	-	-	1	-	-
	G4	-	-	-	-	-
Diarrhoea	G3	-	-	1	-	-
	G4	-	-	-	-	-

TREATMENT RELATED AEs by TREATMENT REGIMEN (all AEs occurring in >2 patients)

Most common treatment related AEs		Bolus	Infusion	Total
Nausea	G1/2	8	6	16
Fatigue	G1/2	6	8	14
Diarrhoea	G1/2	6	2	8
Myelosuppression	G1/2	7	-	7
Mucositis	G1/2	4	5	9
Dyspnoea	G1/2	4	5	9
Abdominal Pain	G1/2	2	2	4
Infection	G1/2	2	4	6
Raised LFTs	G1/2	1	1	2
Vomiting	G1/2	2	-	-

PRIMARY OBJECTIVE: MTD AND DLT DOSE

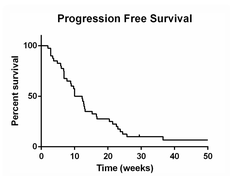
- DLT dose for bolus was 575mg/m^2
- MTD for bolus was 525mg/m^2
- DLT dose for Infusion was not reached at 3600mg/m^2
- MTD dose for Infusion was 3600mg/m^2
- The MTD for both schedules represents a 25% increase in dose intensity

PK DATA

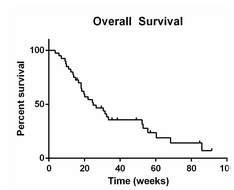
- Limited sampling PK assessment was conducted on all patients
- PK showed substantial inter-patient variability, with no evidence of saturation in CLR, and a trend to linear increase in AUC with dose. 5FU PK in this mixture is similar to 5FU alone
- See Poster 2530, in session Clinical Pharmacology and Experimental Therapeutics, June 5th, 8.00 – 11.30AM: **"Deflexifol** (a novel formulation of 5FU):pharmacokinetics in a phase 1 trial in comparison to 5FU" for more extensive details

RESPONSE RATE

- The response rate at cycle 6 36/40 (90%) of patients
- The overall disease control rate was 24/36 (66.6%; 1 partial response, 23 stable disease, and 12 patients with progressive disease)
- There was no difference in response with higher dose level (p=0.24), prior 5-FU exposure (p=0.55), primary tumour location (colorectal vs non colorectal; p=0.17), or regimen (bolus vs infusion; p=0.14)



Progression Free Survival : Median 11.4 weeks



Overall Survival : Median 24.9 weeks

CONCLUSION

- No grade 4 toxicity in either schedule
- MTD in bolus weekly schedule (525 mg/m^2) exceeds that of current standard LV followed by 5FU
- Proposed phase 2-3 dose is 500mg/m^2, with DLTs as expected for 5FU
- MTD in 46-hour infusion schedule not reached at 3600 mg/m^2 (proposed phase 2 dose is 3000 mg/m^2)
- A significant level of efficacy was seen, given that 80% patients were 5FU-resistant
- Suggests that simultaneous administration of Leucovorin and 5FU as **Deflexifol** might have greater efficacy than LV and 5FU separately
- A phase II study of **Deflexifol** in combination with oxaliplatin is planned

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EMAIL : philipc@uow.edu.au