Abstract #4123

A PHASE II STUDY OF TRIAPINE® IN COMBINATION WITH GEMCITABINE IN PATIENTS WITH UNRESECTABLE OR METASTATIC PANCREATIC CANCER

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ABSTRACT

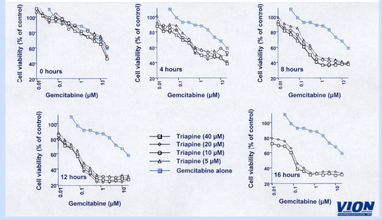
Background: Triapine® is a small molecule that inhibits ribonucleotide reductase at a site distinct from gemcitabine (gem). In tumor cell lines, pre-exposure to Triapine® enhances gem uptake and DNA incorporation, and yields synergistic cytotoxicity. A phase I trial of Triapine® + gem showed that the combination was well-tolerated and produced Triapine® serum concentrations sufficient to modulate gem activity *in vitro* (Ca Chemother Pharmacol, 2004). **Methods:** We conducted a phase II trial of Triapine® + gem in advanced pancreatic cancer pts at 7 centers. Eligible pts were untreated, had measurable disease and ECOG PS 0-2. Triapine® was given by 4-hr infusion followed by gem 1000 mg/m^2 on days 1, 8, and 15 of a 4-week schedule. Since preclinical studies showed longer exposure of Triapine® maximized synergy between the agents, the protocol was amended to administer Triapine® over 24 hrs continuous infusion (CI) prior to gem. Pts were assessed for response q 2 cycles and retreated to progression or toxicity. **Results:** Sixty pts (median age 62, range 37-88) were treated with Triapine® by 4-hr infusion (median 4 cycles, range 1-18). Pt characteristics included M:F 39/21; PS 0/1/2= 25(42%)/ 34(57%)/1(2%); metastatic/locally advanced 72/28%. Eight (15%) patients achieved PR; and 32 (60%) had stable disease. Median survival was 8 mos; 13% are alive at 1 yr. The next 6 pts (median age 54, range 50-69, M/F: 3/3) received Triapine® at a fixed dose of 400mg CI over 24 hrs + gem. Two pts were evaluable for response; 1 pt had PD, 1 pt is on treatment after 14 cycles. Due to excessive myelosuppression the dose of Triapine® CI was reduced to 105 mg/m^2 over 24 hrs. Of 7 pts (median age 60, range 34-73) treated, 2 had PD, 1 was unevaluable, and 4 remain on tx. Triapine® toxicity included hypotension, hypoxia, rash and dyspnea in < 10% of pts. In the 2 CI groups (N=13), the only toxicity attributed to Triapine® was excessive myelosuppression, requiring gem dose reduction in all pts. **Conclusions:** Triapine® + gem shows activity in pancreatic cancer. As predicted by preclinical studies, prolonged exposure (CI) enhances biological effect of Triapine® + gem evidenced by increased myelosuppression without additional toxicities. Further studies are warranted to define the optimal dose of Triapine® CI with gem.

RATIONALE

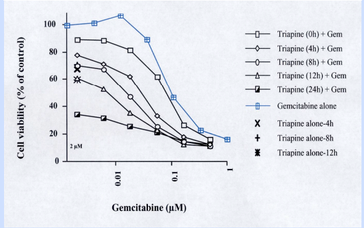
- Triapine® is a potent inhibitor of the M2 subunit of ribonucleotide reductase, a different mechanism of inhibition from gemcitabine, which is an M1 inhibitor
- In vitro Triapine® is 1000x more potent than hydroxyurea and is active in hydroxyurea-resistant cell lines
- Triapine® is a potent iron chelator
- Triapine® inhibits production of deoxyribonucleotides and DNA synthesis
- In vitro, Triapine® exposure to tumor cell lines shows enhanced cellular uptake and DNA incorporation of gemcitabine, as well as synergistic cytotoxicity in a schedule-dependent manner
- Gemcitabine cytotoxicity is attributed to DNA incorporation
- Phase I study of Triapine® plus gemcitabine was well tolerated and established MTD of Triapine with gemcitabine 1000mg/m^2

PRECLINICAL STUDIES

Cytotoxicity of Triapine® (0-16 hours) Followed by Gemcitabine (1 hour), Wash, Assay at 72 hours (KB cells)



Cytotoxicity of Triapine® (0-24 hours) Followed by Gemcitabine (1 hour), Wash, Assay at 72 hours (HTB177 cells)



OBJECTIVES

- Primary:
  - To determine the objective response rate (partial and complete responses based on RECIST criteria) of a regimen of Triapine® and gemcitabine in patients with unresectable or metastatic pancreatic cancer.
- Secondary:
  - To assess the safety of the regimen and feasibility of this regimen in multiple centers.
  - To determine the progression-free interval and survival in this group of patients.

STUDY TREATMENT

- Day 1, 8, 15 of each 28-day cycle:
  - Cohort 1 – Triapine® 105 mg/m^2 IV over 4 hours
  - Gemcitabine 1000mg/m^2 IV over 30 minutes within 2 hours of end of Triapine® infusion
  - Cohort 2a – Triapine® 400 mg IV CI over 24 hours
  - Cohort 2b – Triapine® 105 mg/m^2 CI over 24 hours
  - Gemcitabine 1000mg/m^2 IV over 30 minutes within 1 hour of completing Triapine® infusion
- Disease assessment q 2 cycles
- Maximum cycles = 12

ELIGIBILITY

- Metastatic or unresectable exocrine pancreatic cancer
- No prior cytotoxic chemotherapy or radiotherapy within 4 weeks
- No prior surgery within 3 weeks
- No prior treatment with a non-cytotoxic regimen within 3 weeks
- Measurable disease defined by RECIST criteria
- Life expectancy ≥ 3 months
- ECOG PS of 0 - 2
- Serum creatinine ≤ 2.0 mg/dl, total bilirubin ≤ 2.0 mg/dl, ALT andAST ≤ 3x upper limit of normal (≤ 5x upper limit of normal in case of liver metastases)
- ANC ≥ 1500/μL, Plts ≥ 100,000/μL, Hgb ≥ 9 gm/μL
- No dyspnea at rest or dependence on supplemental oxygen
- No CNS metastases
- No known G6PD deficiency
- Written informed consent

CRITERIA FOR DOSE REDUCTION

- Day 1 gemcitabine doses require normal hematologic values and recovery of non-hematologic toxicity to ≤ grade 1
- Gemcitabine doses reduced within a cycle for ANC <1000 and platelets <75,000
- Gemcitabine and Triapine® doses within cycle held for ≥ grade 2 non-hematologic events, grade 4 ANC or ≥ grade 3 thrombocytopenia
- Skipped doses within cycle not made up
- Triapine® doses reduced for specific Triapine® infusion-related events:
  - Hypoxia, dyspnea
  - EKG changes
  - Hypotension
- Only two dose reductions permitted while on study
- Cohort 2 patients unable to tolerate treatment for 3 consecutive weeks may be converted to a 2 week on, 2 week off schedule

DEMOGRAPHICS

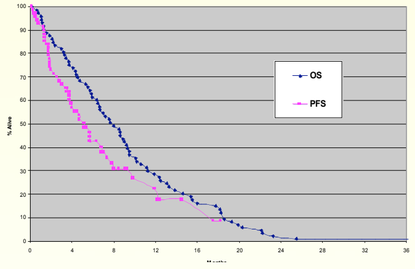
	Cohort 1	Cohort 2a	Cohort 2b
Patients treated	60	6	7
Sex (male/female)	39/21 (65%, 35%)	3/3 (50%,50%)	4/3 (57%, 43%)
Median age (range)	62 (37-88)	54.5 (50-69)	60 (34-73)
ECOG performance status N(%)			
0	25(42%)	1(17%)	1(14%)
1	34(57%)	5(83%)	6(86%)
2	1(2%)	0	0
Unresectable disease	7(12%)	0	1(14%)
Metastatic disease	53(88%)	6(100%)	6(86%)

CLINICAL ACTIVITY

Overall Best Response - N (%)

Response	Cohort 1 N=60	Cohorts 2a & 2b N=13
CR	0	0
PR	11(21%)	0
SD	29(55%)	7(78%)
PD	13(24%)	2(22%)
NE	7(12%)	4(31%)

SURVIVAL CURVE



TREATMENT TOLERABILITY

	Cohort 1	Cohorts 2a & 2b
Median # cycles (range) received per patient	4 (1-18)	2 (1-18)
# patients (%) off study due to toxicity	8 (13%)	4(31%)
Total # cycles administered	324	53
Total # cycles given at full doses	222	0
# patients (%) requiring dose reduction:		
•Gemcitabine	26(43%)	13(100%)
•Triapine®	2 (3%)	1(8%)

TOXICITIES ≥GR 3

Possibly Related to Treatment

EVENT AND GRADE	Cohort 1- N(%) (N=60)		Cohort 2a & 2b - N(%) (N=13)	
	GR 3	GR 4	GR 3	GR 4
Febrile Neutropenia	0	0	1(8%)	1(8%)
Neutropenia	17(28%)	6(10%)	0	11(85%)
Thrombocytopenia	11(18%)	2(3%)	3(23%)	4(31%)
Anemia	8(13%)	2(3%)	1(8%)	2(15%)
Nausea	3(5%)	0	2(15%)	0
Vomiting	1(2%)	0	2(15%)	0
Fatigue	8(13%)	0	1(8%)	0
Diarrhea	2(3%)	0	1(8%)	0
Increased ALT	2(3%)	0	0	0
Hyperbilirubinemia	0	0	1(8%)	0
Dyspnea	1(2%)	1(2%)	0	2(15%)
Syncope	0	0	1(8%)	0

Possible Triapine® Infusion-related Toxicities*

Event	Cohort 1 N=60		Cohort 2a & 2b N=13	
	GR 3	GR 4	GR 3	GR 4
Hypotension	0	0	0	0
Hypoxia	3(5%)	0	0	0
Rash	0	0	0	0
Dyspnea	1(2%)	1(2%)	0	1(8%)

CONCLUSIONS

- The 4-hour regimen of Triapine® followed by gemcitabine is safe and produces a toxicity profile similar to historical data of gemcitabine alone with the exception of transient hypoxia
- 4-hour infusion of Triapine® followed by gemcitabine demonstrates activity in advanced pancreatic cancer
- 49% (30/61) patients with elevated CA19-9 experienced ↓ ≥ 50% from baseline
- 24-hour continuous infusion Triapine® causes significant myelosuppression resulting in dose reduction of gemcitabine

FUTURE DIRECTIONS

- Preclinical data indicates that longer exposure Triapine® prior to gemcitabine may enhance anti-tumor effect
- Oral formulation of Triapine® is being developed for future combination chemotherapy trials to extend the duration of Triapine® exposure prior to administration of nucleoside analog therapy
- Phase I combination therapies with Triapine® for pancreatic cancer and ovarian cancer are being developed