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Phase I trial of daily triapine in combination with cisplatin chemotherapy for advanced-stage malignancies

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Abstract

Purpose—Advanced-stage malignancies have increased deoxyribonucleotide demands in DNA replication and repair, making deoxyribonucleotide supply a potential exploitable target for therapy based on ribonucleotide reductase (RNR) inhibition.

Methods—A dose-finding phase I trial was conducted of intravenous (i.v.) triapine, a small-molecule RNR inhibitor, and cisplatin chemotherapy in patients with advanced-stage solid tumor malignancies. Patients received dose-finding levels of i.v. triapine (48–96 mg/m^2) and i.v. cisplatin (20–75 mg/m^2) on 1 of 3 different schedules. The primary endpoint was to identify the maximum tolerated dose of a triapine-cisplatin combination. Secondary endpoints included the rate of triapine-cisplatin objective response and the pharmacokinetics and bioavailability of a single oral triapine dose. (clinicaltrials.gov number, NCT00024323)

Results—The MTD was 96 mg/m^2 triapine daily days 1–4 and 75 mg/m^2 cisplatin split over day 2 and day 3. Frequent grade 3 or 4 adverse events included fatigue, dyspnea, leukopenia, thrombocytopenia, and electrolyte abnormalities. No objective responses were observed; 5 (50%) of 10 patients treated at the MTD had stable disease. Pharmacokinetics indicated an oral triapine bioavailability of 88%.

Conclusions—The triapine-cisplatin combination may be given safely in patients with advanced-stage solid tumor malignancies. On the basis of these results, a phase I trial adequately powered to evaluate oral triapine bioavailability in women with advanced-stage uterine cervix or vulvar cancers is underway.

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CONFLICTS of INTEREST

Conflict of Interest: The authors declare that they have no conflict of interests.

Keywords

triapine; cisplatin; phase I clinical trial; advanced malignancies; dose-limiting toxicity; maximum tolerated dose; oral bioavailability

INTRODUCTION

Advanced-stage malignancies are clinically and phenotypically diverse, which often obscures early-phase solid tumor clinical trial efforts to discover beneficial patient-specific therapies. Despite this issue of disease heterogeneity, ribonucleotide reductase (RNR) is a critical enzyme *in all cells* as it catalyzes the *de novo* conversion of ribonucleotides to their corresponding deoxyribonucleotides, which are critical precursors for DNA synthesis (dNDPs) [1]. In advanced-stage malignancies, dysregulation of RNR, an important regulator of DNA replication and DNA damage repair [2–4], has been attributed to a number of mechanisms, including disrupted protein-protein stabilization, unchecked cell cycle-phased expression, and aberrant allosteric feedback [5–8]. RNR overexpression has also been implicated in facile DNA damage repair (such as in uterine cervix cancer [9,10]), providing a strong rationale for the clinical development of new drug combinations that inhibit RNR dNDP output and imbalance dNDP demand-supply intracellular economics.

RNR generates *de novo* dNDPs by proton-coupled electron transfer from two tyrosyl radical-sites (M2 or M2b [p53R2] subunits) to active-sites (M1 subunits) [7,8]. Quashing the M2/M2b radical renders RNR inactive [11]. Triapine (also known as 3-aminopyridine-2-carboxaldehyde thiosemicarbazone [3-AP]) is an equipotent RNR M2/M2b anticancer agent with inhibitory activity in preclinical models such as uterine cervix cancer [2–4]. Preclinical studies have shown that combining RNR inhibitors with platinum chemotherapy agents, which induce DNA damage through formation of DNA adducts and cross-linking, potentiates chemotherapeutic cytotoxicity [4]. Targeted pharmacologic RNR blockade by triapine in advanced-stage uterine cervix cancer patients has led to effective disease control (96%) and long-term survival (82%) among women treated by a radiation-cisplatin-triapine combination [12–14]. For this reason, there is intense interest in the pharmacokinetic and safety data of triapine-cisplatin co-administration, especially as it pertains to on-going and future clinical development of oral triapine-cisplatin combination therapy.

The VION-021 phase I trial was a multicenter, dose-escalation trial of an intravenous (i.v.) triapine and i.v. cisplatin combination in adults with advanced-stage cancer refractory to standard therapy or for which no curative therapy existed. The primary endpoint was determination of the maximum tolerated dose (MTD) of the triapine-cisplatin combination [15]. Herein, we report for the first time, the triapine-cisplatin tolerability, efficacy and pharmacokinetic results, including the first-ever single-dose oral triapine administration data. These findings are important as they provide context for an ongoing early-phase I clinical trial determining the bioavailability of five-times weekly oral triapine and once-weekly i.v. cisplatin plus radiotherapy among women with advanced-stage gynecological malignancies. (clinicaltrials.gov number, NCT02595879).

MATERIALS and METHODS

Study Design and Treatment

This was an open-label dose-finding phase I trial of once-daily i.v. triapine in combination with once-weekly i.v. cisplatin chemotherapy, exploring three schedules as indicated in Table 1 (clinicaltrials.gov number, NCT00024323). Patients were enrolled on study and dose escalation proceeded using a Fibonacci 3+3 cohort trial design, where a single drug-related adverse event in an initial three-patient cohort prompted expansion to six patients in order to verify a 33% toxicity rate. Dose-finding continued if no other adverse events occurred (i.e., two or fewer of six patients); otherwise, dose-finding discontinued. A MTD was declared when six patients had been treated with ≤ 1 instance of an observed adverse event. Adverse events were scored according to the Common Terminology Criteria for Adverse Events (CTCAE, version 2.0). Adverse events indicating dose-limiting toxicity (DLTs) included all severe or life-threatening toxicities, grade 3 non-hematologic toxicities lasting more than 24 hours, all grade 4 non-hematologic toxicities, persistent grade 2 toxicities lasting more than one week, grade 2 neurotoxicity, tinnitus, or loss of hearing, or any grade persistent toxicities requiring delay of scheduled treatment by more than two weeks.

Participants received i.v. triapine at an initial dose of 96 mg/m^2 for five daily doses (Table 1). Vion Pharmaceuticals Inc. supplied i.v. triapine in vials of 50 mg, which was diluted for two-hour infusion per the manufacturer's instruction. Infusion of i.v. triapine occurred after the completion of i.v. cisplatin administration. In the bioavailability phase of this trial, participants received oral triapine in escalating doses on day 1 only (Table 1), and then received i.v. triapine for the remainder of their treatment course. Vion Pharmaceuticals Inc. supplied oral triapine in 50 mg size 1, hard gelatin, white opaque capsules.

Participants received i.v. cisplatin over one hour between 25 to 75 mg/m^2 for one weekly dose (Table 1). Cisplatin was obtained by commercial vendor and diluted per the manufacturer's instruction. For the 50 and 75 mg i.v. cisplatin dose levels, the dose was split over two consecutive days.

Eligibility and Enrollment

The trial was open to women and men 18 years of age or older who had a diagnosis of a measurable advanced-stage malignancy refractory to standard therapy or for which no curative therapy existed. Patients must have had an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1; a life expectancy greater than three months; adequate kidney, liver, and bone marrow capacity as determined by laboratory assessment; and be practicing adequate contraception or abstinence. Female patients of childbearing potential must have had a negative pregnancy test within two weeks before study drug administration. Patients must not have had active infections, severe hearing impairment, active central nervous system metastases, presence of any other life-threatening illness, prior severe allergic reaction to cisplatin, or poor nutrition (i.e., albumin < 2.5 g/dL). Participants must have had prior treatment for their malignancy, meaning at least three weeks of convalescence after prior surgery, last dose of chemotherapy, and/or last dose of radiation therapy. This also included at least two-week recovery from hormonal therapy or biologic

anticancer therapy. Persistent toxicities from prior therapies must not have been greater than grade 1. Patients must not have had cisplatin or platinum analogue within three months of starting study drug administration. Patients whose prior therapy included triapine were not re-challenged with a triapine-cisplatin treatment. All patients must have provided written informed consent prior to initiating trial treatment.

Assessments

Medical histories, physical examinations including performance status, urinalysis, serum chemistries, and complete blood counts were obtained at baseline, before the first dose of each weekly triapine-cisplatin cycle, once each interval week, and at off-study. Computed tomography scans of the chest and abdomen were obtained every cycle. Magnetic resonance imaging of the brain, bone scan, or serum tumor marker were obtained every cycle, as clinically indicated for a patient's disease and status.

Pharmacokinetics

Peripheral blood samples were collected, and serum was separated and stored at −20 °C. On the day of oral dosing, blood samples were obtained immediately before dosing, and at 10, 20, and 30 min, and 1, 2, 4, 6–8, and 24 hours after dosing. On the day of i.v. triapine administration, blood samples were obtained immediately before the start of the infusion, during the infusion at 15 and 30 min, 1, 1.5 hours, and at the end of infusion (2 hours), and post-dosing at 2 hours 15 min, 2 hours 30 min, 2 hours 45 min, 3, 6, and 8 hours after the start of infusion.

Serum samples (0.5 mL) were extracted with 1.0 mL of 4 mM EDTA in methanol. After centrifugation, the extract was concentrated to dryness and reconstituted with 0.25 mL of a solvent consisting of 10% acetonitrile and 90% mobile phase containing 20 mM phosphate buffer (pH 3.0), 15 mM 1-heptane sulfonic acid and 1 mM EDTA. The reconstituted solution was further centrifuged, and then, the supernatant was injected into a high performance liquid chromatography (HPLC) system. External calibration standards were prepared in pooled control human serum, and processed identically to test samples and independently prepared quality control samples. The assay had a nominal curve range of 0.02 to 10 μg/mL.

Study Oversight

The principal investigators (JM, MS) designed the trial and its dose escalation/dose reduction levels. The drug manufacturer supplied triapine and collected data, but did not participate in the study design, analysis, or manuscript preparation. An independent quality assurance audit (Prologue Research International, Inc.) documented in compliance with all applicable regulations. All participating sites received institutional review board approval prior to first dose administration. A manuscript publication team (CK, EC, JB, PI) subsequently compiled, authenticated, and analyzed the trial data for manuscript publication.

Evaluation of Clinical Activity and Statistical Analysis

Tumor measurement criteria, according to the guidance in the Response Evaluation Criteria in Solid Tumors (RECIST, version 1.0), were applied at baseline and at each subsequent

treatment cycle by the investigators for response and to establish disease progression [16]. No formal statistical analyses or comparisons were performed.

RESULTS

Patients

Patients were eligible to undergo triapine-cisplatin treatment from June 2001 through May 2004. During this period, there were three groups studied in the dose-finding portion of this trial (Table 1). A total of 30 patients were enrolled to receive triapine-cisplatin, and 25 patients were evaluated with regard to the primary endpoint of drug-drug co-administration safety. Patient characteristics at baseline appear in Table 2. All patients had surgery (n = 25) for treatment of their advanced-stage malignancy, and the majority had had prior cytotoxic chemotherapy (n = 23) or palliative radiation therapy (n = 15) before enrolling on this trial. Prior hormonal therapy (n = 5) or immunotherapy (n = 3) were uncommon. Five screened patients did not receive any triapine-cisplatin; all five of these patients were excluded from safety evaluations.

Safety

Table 3 lists the most common adverse events encountered in all three triapine-cisplatin treatment groups. The most frequent adverse events included grade 1 constipation or nausea; grade 2 anemia; grade 3 asthenia or dyspnea; and grade 3 or 4 leukopenia or thrombocytopenia. The intensity of the hematologic adverse events was greatest in the daily × 5 every two-week schedule, prompting first a reduction in treatment interval from two weeks to three weeks, and prompting second, a reduction in triapine administrations from five days to four days (Table 1). The triapine (96 mg/m^2)—cisplatin (75 mg/m^2) dose level was declared the MTD, where the main side effects were reversible asthenia, dyspnea, leukopenia, and thrombocytopenia.

Dose reductions of triapine occurred in eight patients (32%) after the first cycle. Dose reductions of cisplatin occurred in three patients (12%) after the first cycle. During triapine-cisplatin treatment, four (16%) discontinued therapy early. The reasons for treatment discontinuation included toxicity (asthenia) in one patient, new unrelated clinical diagnoses (congestive heart failure, atrial fibrillation) in two patients, and patient preference in one patient. The median number of treatment cycles administered was two cycles (range 1 to 12). There were no triapine-cisplatin treatment-related deaths. Fatal adverse events occurred in three (12%) patients, with two of these events being attributable to disease progression within 30 days after receipt of triapine-cisplatin treatment and one event resulting from congestive heart failure complicated by sepsis.

Efficacy

For patients who received at least one cycle of therapy, there were no objective responses (complete or partial response) to triapine-cisplatin treatment. Stable disease occurred in eight (32%) patients. The durations of stable disease were 1, 4, 4, 4, 5, 5, 7, and 8 months. In the MTD cohort, five (of 10, 50%) best responses of stable disease were documented; a 6-month duration of stable disease was observed in one (10%) patient with breast cancer.

Progression of disease was recorded in eight (32%) patients. In three (12%) others, symptomatic decline precluded documentation of disease status, and thus, were counted as having had disease progression. Response was not evaluated after study entry in six (24%) patients.

Pharmacokinetics and Oral Bioavailability

Pharmacokinetic parameters calculated by noncompartmental methods are provided in Table 4. Peak concentrations (C_{max}) of triapine were recorded up to 240 minutes after oral administration. Triapine concentrations declined with an approximate half-life of one hour after i.v. administration and two hours after oral administration. The average oral bioavailability of triapine was 88%.

DISCUSSION

This phase I trial showed that the addition of a RNR inhibitor to cisplatin cytotoxic chemotherapy was tolerable, when given every three weeks at a dose of triapine (96 mg/m^2) daily for four days and cisplatin (75 mg/m^2) over two days, among patients with advanced-stage solid tumor malignancies.

A triapine-cisplatin combination has been evaluated in trials of platinum-resistant ovarian cancer [17] and of uterine cervix cancer when added to pelvic radiation therapy [12,13], demonstrating activity at various doses and schedules. In the present study, triapine was given on day 1, prior to the cycle's doses of cisplatin, to take advantage of the potential synergy from RNR inhibition before platinum-mediated DNA damage. Daily triapine dosing was selected based on the hypothesis that repeated RNR inhibition might exert a more sustained block in dNDP supply when needed most for cisplatin-DNA adduct repair, resulting in enhanced cytotoxic effects. This trial's rate of triapine-cisplatin stable disease (50%) at the MTD dose level matched the rate described in a triapine-cisplatin trial for response plus stable disease in platinum-resistant ovarian cancer (50%) [17]. However, this trial's rate of patient pretrial disease progression was not collected, and therefore, any observed stable disease period may not be attributed to a triapine-cisplatin biological effect. The fact that nearly all patients in this trial eventually had disease progression while receiving triapine-cisplatin suggests an undiscovered acquired triapine-cisplatin resistance.

Patients in this trial were a mixed solid tumor population, not selected for platinum sensitivity and sensitization. Unknown at the time of this trial's design, triapine when given before cisplatin disrupts RNR activity with initial cytostatic effect, subsequently promotes enhanced recovery of RNR activity 18–24 hours later, accelerates cisplatin-DNA adduct repair, and increases the relative proportion of cancer cells surviving triapine-cisplatin exposure [17]. When given in an opposite sequence, triapine given after cisplatin impedes RNR activity with cytotoxic effect, halts dNDP supply by RNR when most critical to DNA damage repair, and potentiates cisplatin-mediated cytotoxicity [17]. In clinical trials of triapine-cisplatin-radiation therapy in women whose uterine cervix cancers overexpress RNR [12,13], and where doses of i.v. triapine (25 mg/m^2) are administered after radiation (180 cGy) on days 1, 3, and 5 or after cisplatin (day 2, 40 mg/m^2) on days 3 and 5, irradiated

disease most often completely resolves (96%) and cisplatin-then-triapine treated-only extrapelvic metastatic disease measurably responds.

Triapine-cisplatin, as administered in this trial, was well tolerated and resulted in reversible asthenia, dyspnea, leukopenia, and thrombocytopenia. Because triapine might disrupt available intracellular nucleotide pools and induce extracellular nucleoside salvage [18], other normal cells such as skeletal muscle might expend intracellular resources to furnish demanded nucleosides, resulting in the fatigue observed on trial. Triapine is also known to increase methemoglobin levels through its iron-chelating properties [19], which putatively lowers oxygen-carrying capacity of blood, and this may be a particularly relevant issue in patients with low pulmonary reserve whose dyspnea may be exacerbated. Whether the dyspnea in this trial can be attributed to a triapine-methemoglobin phenomenon remains unknown, as methemoglobin levels were not collected in patients on this trial. Of note is the fact that there were no side effects directly attributable to cisplatin, such as renal toxicity or ototoxicity. In other triapine-cisplatin studies, the risks of cisplatin-mediated toxicities have also been minimal [12,13,17].

Limitations of this phase I study include the small sample size, which restricts an ability to assess therapeutic response; potential investigator bias due to arbitrary adjustments in triapine-cisplatin exposure following adverse events; and recall bias due to the protracted time from study completion to study publication.

In conclusion, this phase I trial provides further evidence that the combination of triapine, a RNR inhibiting agent, and cisplatin, a cytotoxic chemotherapy agent, may be given together safely in patients with advanced-stage solid tumor malignancies. On this basis, a confirmatory oral bioavailability phase I trial has been initiated to study five-times weekly oral triapine and once-weekly i.v. cisplatin plus radiation therapy in women with advanced-stage gynecological malignancies.

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Table 1

Dose escalation and extent of drug exposure.

Daily × 5 q 2 weeks schedule (n = 8)					
Dose Level	**Triapine Dose (mg/m^2/day)**	**Cisplatin Dose (mg/m^2)** *	**No. of new patients**	**Total no. of patients treated** †	**Total no. course administered**
−1b	84	20	0	2	2
−1a	84	25	0	2	8
1	96	25	5	5	9
2	96	37.5	3	3	6
Daily × 5 q 3 weeks schedule (n = 2)					
Dose Level	Triapine Dose (mg/m^2/day)	Cisplatin Dose (mg/m^2) **	No. of new patients	Total no. of patients treated †	Total no. course administered
−1	84	37.5	0	1	3
1	96	25	0	1	1
2	96	37.5	2	3	5
Daily × 4 q 3 weeks schedule (n = 15)					
Dose Level	Triapine Dose (mg/m^2/day)	Cisplatin Dose (mg/m^2) ***	No. of new patients	Total no. of patients treated †	Total no. course administered
−2	48	40	0	1	1
−1b	72	50	0	1	1
−1a	72	75	0	3	9
1	96	50	5	5	24
2	96	75	10 ‡	10	26

† Some patients were treated at more than one dose level.

* Cisplatin dose administered on day 3.

** Cisplatin dose divided over day 3 and day 4.

*** Cisplatin dose divided over day 2 and day 3.

‡ Seven of 10 patients at cycle 1 consented to treatment by a single dose of oral triapine.

Table 2

Patient and disease characteristics ($n = 25$)

Characteristic	No. of patients	%
Age (years)		
30–39	1	4
40–49	5	20
50–59	6	24
60–69	6	24
70–79	6	24
80–89	1	4
Sex		
Female	11	44
Male	14	56
Race		
White	22	88
Black or African	2	8
American Indian/Alaskan	1	4
Ethnicity		
Hispanic	4	16
Non-hispanic	21	84
Performance		
0	10	40
1	15	60
2	0	0
Disease Site		
Lung	5	20
Breast	3	12
Colon	3	12
Prostate	2	8
Pancreas	2	8
Bladder	1	4
Esophageal	1	4
Kidney	1	4
Liver	1	4
Nasal	1	4
Oropharynx	1	4
Sarcoma	1	4
Tonsil	1	4
Thyroid	1	4
Adenocarcinoma, not specified	1	4

Table 3

Adverse events by grade with any relationship to triapine-cisplatin (n = 25).*

	Grade				
	1	2	3	4	5
Toxicity	**No.**	**No.**	**No.**	**No.**	**No.**
Allergy/Immunology	0	0	1	0	0
Blood/Bone marrow (other)	4	1	2	0	0
Anemia	2	11	4	0	0
Febrile neutropenia	0	0	0	0	0
Leukopenia	1	0	6	14	0
Thrombocytopenia	2	4	6	3	0
Cardiovascular	17	4	11	0	0
Constitutional (body as a whole)	31	20	10	1	0
Fatigue	4	8	11	1	0
Dermatology/Skin	9	5	0	0	0
Endocrine/Special Senses	4	8	0	0	0
Tinnitus	2	1	0	0	0
Hearing Loss	2	2	0	0	0
Gastrointestinal (general)	26	11	5	0	0
Constipation	7	3	1	0	0
Diarrhea	4	1	2	0	0
Dysphagia	0	1	0	1	0
Emesis	3	5	2	0	0
Nausea	5	4	6	0	0
Infection	0	2	1	1	0
Metabolic/Nutritional	29	37	11	2	0
Creatinine increased	4	1	0	0	0
Hypokalemia	4	0	3	0	0
Hyponatremia	3	0	3	1	0

	Grade				
	1	**2**	**3**	**4**	**5**
Toxicity	**No.**	**No.**	**No.**	**No.**	**No.**
Musculoskeletal	4	6	0	0	0
Neurology	27	13	4	0	0
Respiratory System	22	9	4	1	0
Dyspnea	3	2	6	0	0
Hypoxia	1	0	1	0	0
Renal/genitourinary	2	2	3	0	0
Sexual/reproductive function	0	0	0	0	0
Worst non-hematologic	213	145	85	8	0
Worst hematologic	9	16	18	17	0

* Patients may have had more than one adverse event.

Abbreviations: No. = number

Table 4

Pharmacokinetic variables (mean (SD)) of intravenous or oral triapine.

Day 1 of daily × 4 q 3 weeks schedule (n = 7)							
Triapine	**AUC (h* mg/L)**	**C_{max} (μg/mL)**	**C_{max}/Dose (μg/L/mg)**	**T_{max} (h)**	**Half-life (h)**	**CL/F (L/h)**	**Bioavailability (%)**
96 mg/m^2 I.V. (N=6)	3.92 (1.97)	1.49 (0.63)	8.24 (4.48)	80	0.92 (0.33)	57.5 (25.0)	-
50 mg P.O. (N=3*)	0.89 (0.78)	0.13 (0.18)	2.67 (3.59)	3.9 (2.1)	2.7 (1.4)	103 (92)	102 (105)
100 mg P.O. (N=4)	1.47 (0.86)	0.26 (0.08)	2.55 (0.83)	1.8 (0.6)	1.7 (1.0)	87.1 (27.1)	80.2 (16.8)
Total P.O. (N=7*)	-	-	2.60 (2.15)	2.7 (1.7)	2.1 (1.2)	94.1 (57.3)	87.6 (49.9)

Abbreviations: AUC = area under the curve; C_{max} = maximum plasma concentration; CL/F = apparent clearance with F=1 for the I.V. patients; T_{max} = time to reach maximum plasma concentration; I.V. = intravenous; P.O> = oral;

*One subject less for bioavailability.