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# Phase I and pharmacokinetic study of Triapine®, a potent ribonucleotide reductase inhibitor, in adults with advanced hematologic malignancies

Ivana Gojo[a,*], Michael L. Tidwell[a], Jacqueline Greer[b], Naoko Takebe[a], Karen Seiter[c], Mary F. Pochron[a], Bonny Johnson[d], Mario Sznol[d], Judith E. Karp[b]

[a] *University of Maryland Marlene and Stewart Greenebaum Cancer Center, 22 S. Greene St., Baltimore, MD 21201, United States*
[b] *The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, United States*
[c] *New York Medical College, Valhalla, NY, United States*
[d] *Vion Pharmaceuticals Inc., New Haven, CT, United States*

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**Abstract**

Triapine®, a potent inhibitor of ribonucleotide reductase, has demonstrated anti-leukemia activity in pre-clinical models. We conducted a Phase I study of Triapine administered as a 2 h infusion for 5 days in 25 adults with advanced leukemias. We established that Triapine at 96 mg/m$^2$ once a day can be given safely on days 1–5 and 15–19 or 1–5 and 8–12 of a 4-week cycle. When administered twice a day on days 1–5 and 8–12, the maximum tolerated dose of Triapine appears to be 64 mg/m$^2$, although the true criteria for DLT were not met by protocol definition. No CR or PR were observed, but 76% of patients had a >50% reduction in white blood cell counts. At all dose levels, the peak plasma concentration of Triapine (2.2–5.5 μM) was above levels required to achieve *in vitro*/*in vivo* leukemia growth inhibition. Based on these data, we conclude that Triapine warrants further investigation in hematologic malignancies.


*Keywords:* Ribonucleotide reductase; Triapine; Acute myeloid leukemia; Chronic myeloid leukemia; Myeloproliferative disorders

## 1. Introduction

Treatment of refractory and relapsed acute leukemias and high-risk myelodysplasias remains a challenge. While intensive multi-chemotherapeutic approaches have had some limited success, overall, there is a substantial need for developing and testing novel therapeutics [1]. Since leukemia cells are characterized by a rapid proliferation rate, one of the strategies to inhibit leukemia cell proliferation is to target the limiting step in the DNA synthesis. Ribonucleotide reductase (RR) catalyses the conversion of ribonucleotides to deoxyribonucleotides and is, therefore, a critical enzyme in the process of DNA synthesis and repair [2]. Its increased activity has been linked to tumorigenesis, invasive potential, and drug resistance [3–10]. Thus, RR represents an attractive therapeutic target and, over the years, multiple chemotherapeutics inhibiting different subunits of RR have been developed and tested clinically for their anti-leukemia activity [11].

Mammalian RR is an α2β2 heterodimer which is composed of two subunits: a regulatory, nucleotide binding site M1 subunit, and an inducible, catalytic M2 subunit which contains non-heme iron and a tyrosyl free radical, which are required for the enzymatic reduction of ribonucleotides [12,13]. The M2 subunit is inhibited by hydroxyurea (HU) and the new α-(*N*)-heterocyclic carboxaldehyde thiosemicarbazone (HCT) derivative Triapine [5,14,15]. Hydroxyurea has been used clinically for three decades, mainly in the settings of hematologic malignancies and sickle cell anemia, however, the oral route of administration and consequent

* Corresponding author. Tel.: +1 410 328 2594; fax: +1 410 328 6896.
*E-mail address:* igojo@umm.edu (I. Gojo).

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pharmacokinetic variability, coupled with other characteristics of the drug such as low potency against RR and the ease of regeneration of the tyrosyl free radical with resultant rapid reversal of HU-induced RR inhibition, resulted in limited clinical activity [5,15–21]. Triapine is a 100–1000 times more potent RR M2 subunit inhibitor than HU which relates in part to its ability to both chelate iron and quench the tyrosyl free radical [14,22–27]. As such, Triapine has shown marked cytotoxicity against hematopoietic cell lines *in vitro* and *in vivo*, including HU-resistant L1210 leukemia cells, was curative for some mice, and when combined with other DNA-damaging agents exhibited synergistic activity against L1210 leukemia [14,22–24,28].

Based on the anti-tumor activity demonstrated in pre-clinical studies, a number of clinical studies exploring different doses and schedules of Triapine administration were initiated [29–32]. In a Phase I study in patients with solid tumors, Triapine administered at a dose of 96 mg/m$^2$ by 2 h intravenous (IV) infusion for 5 days on an every-other week schedule demonstrated an acceptable safety profile, serum concentrations that surpass *in vitro* tumor growth inhibitory concentrations ($C_{max}$ 8 μM, $T_{1/2}$ 35 min–3 h) were achieved for a brief period of time each day, and anti-tumor activity was recorded [31]. Based on the above data, we initiated a Phase I study of Triapine in patients with advanced leukemias initially using the same dose and schedule of administration. However, pre-clinical and early clinical data suggested that Triapine-mediated anti-tumor effects may be better when RR is inhibited throughout most or all of the day for several days consecutively. Consequently, the study was amended and subsequent cohorts received Triapine once or twice a day for 5 days, 2 weeks in a row [22,23]. Limited pharmacokinetic sampling was performed to determine the peak serum concentrations, half-life of the drug and the total area under the concentration–time curve.

## 2. Patients and methods

### 2.1. Patient eligibility

Adult patients (≥18 years old) with relapsed/refractory acute leukemias including acute myeloid leukemia (AML), acute lymphoid leukemia (ALL), chronic myeloid leukemia (CML) in accelerated or blast phase, poor-risk (IPSS ≥ 1.5) myelodysplasia (MDS), and aggressive (transformed) myeloproliferative disorder (MPD) for whom no standard therapies were anticipated to result in a durable remission were considered eligible for the study. Other eligibility criteria included an ECOG performance status ≤2; serum creatinine ≤2 mg/dl; AST, ALT, alkaline phosphatase levels ≤5× upper limit of normal (ULN); serum total bilirubin ≤2 mg/dl; PT/PTT ≤1.5× ULN; negative pregnancy test and willingness to practice contraception; and no chemotherapy for 3 weeks, no radiation therapy for 2 weeks, and no growth factors or other biological agents for 1 week prior to entering the study and recovery from the toxic effects of that therapy, unless there was evidence of rapidly progressive disease. Patients who were on hydroxyurea to control peripheral blood leukemic cell counts had to stop taking hydroxyurea for at least 72 h prior to initiation of the treatment on this protocol. Patients with curative treatment options such as allogeneic stem cell transplantation (allo SCT), active central nervous system leukemia, severely compromised cardiac and/or pulmonary function, or any other coexisting medical or psychiatric conditions that could interfere with study procedures were excluded from the study. All patients gave signed informed consent indicating that they were aware of the investigational nature of this study according to the University of Maryland School of Medicine and New York Medical College IRB policies.

### 2.2. Treatment

Treatment was administered in an outpatient setting unless the patient was hospitalized for other reasons or for safety (*e.g.* high tumor burden with risk for tumor lysis syndrome, rapidly progressive disease, *etc.*). Patients were assessed on each treatment day and monitored during and after the Triapine 2 h long infusion, and then at least once or twice weekly or more as clinically indicated. Triapine was supplied by Vion Pharmaceuticals Incorporated, New Haven, CT. The first patient cohort received Triapine dose of 96 mg/m$^2$ daily for 5 days every other week (days 1–5 and 15–19). This dose and schedule was selected based on the safety data from a solid tumor study and the expanded cohort of nine patients was treated to confirm its safety in the setting of hematologic malignancies [31]. As no dose limiting toxicity (DLT) was encountered, and based on pre-clinical and early clinical data suggesting that more prolonged RR inhibition may be required for Triapine activity, in particular, the observation that in some patients after initial reduction leukemia blasts recovered prior to the planned initiation of the second week of treatment beginning on day 15, the study was amended to incorporate the evaluation of a daily ×5 weekly ×2 schedule and an every 12 h × 5 days schedule at increasing dose levels in order to identify the maximum tolerated dose (MTD). Therefore, in subsequent cohorts, Triapine was administered daily for 5 days, 2 weeks in a row (days 1–5 and 8–12). Initially, Triapine was administered at the same dose of 96 mg/m$^2$ once a day on this schedule. In subsequent cohorts, Triapine was administered twice a day starting at 48 mg/m$^2$ (the same total dose) and the dose was escalated in the absence of DLTs. Intrapatient dose escalation was allowed, however, all patients at the previous dose level had to complete 2 weeks of observation before dose escalation could proceed. Each treatment cycle lasted 28 days and treatment delays of up to 2–3 weeks were permitted for subsequent cycles. Subsequent cycles were administered in the absence of progressive disease.

As already discussed above, nine patients were treated in the first cohort to establish the safety of dose/schedule