ARTICLE

Oral arsenic trioxide ORH-2014 pharmacokinetic and safety profile in patients with advanced hematologic disorders

Farhad Ravandi,[1] Iphigenia Koumenis,[2] Anandhi Johri,[2] Martin Tallman,[3] Gail J. Roboz,[4] Stephen Strickland,[5] Guillermo Garcia-Manero,[1] Gautam Borthakur,[1] Kiran Naqvi,[1] Meghan Meyer,[1] Madhu Pudipeddi,[2] Sirish Nidarmarthy,[2] Kris Vaddi[2] and Hagop Kantarjian[1]

[1]M.D. Anderson Cancer Center, Houston, TX; [2]Orsenix, Wilmington, DE; [3]Memorial Sloan Kettering Cancer Center, New York, NY; [4]Weill Cornell Medicine, New York, NY and [5]Vanderbilt University Medical Center, Nashville, TN, USA

Ferrata Storti Foundation

Haematologica 2020
Volume 105(6):1567-1574

ABSTRACT

Daily intravenous arsenic trioxide administered with all-trans retinoid acid, the standard-of-care for acute promyelocytic leukemia, is costly and challenging to administer. ORH-2014 is a novel, oral arsenic trioxide formulation, consisting of micron-size drug particles with rapid dissolution and high bioavailability. We conducted a multicenter phase 1 dose-escalating study in patients with advanced hematologic malignancies. Twelve patients received ORH-2014 at 5 mg (n=3), 10 mg (n=6), or 15 mg (n=3) orally once a day (fasted state). Objectives were to assess the safety, tolerability and pharmacokinetics of ORH-2014 to support a dose recommendation for future trials. The median age of the patients was 77 years (range: 45-81) and they had received a median of two (range: 1-5) prior therapies. There were no dose limiting toxicities and no drug-related severe adverse events, except one grade III QT prolongation occurring beyond the dose limiting toxicity assessment period and resolving after treatment interruption. ORH-2014 steady-state plasma concentration was reached on day 15. ORH-2014, 15 mg C_{max} was comparable to the calculated approved dose of intravenous arsenic trioxide (mean [% coefficient of variation]: 114 [21%] *vs.* 124 [60%] ng/mL) and area under the curve from 0 to 24 hours was 2,140 (36%) *versus* 1,302 (30%) h*ng/mL. These results indicate that ORH-2014 at 15 mg is safe, bioavailable, and provides the required arsenic exposure compared to intravenous arsenic trioxide at the approved dose (0.15 mg/kg); this ORH-2014 dose is recommended for future trials. (*NCT03048344; www.clinicaltrials.gov*).

Introduction

As a rare subtype of acute myeloid leukemia (AML), acute promyelocytic leukemia (APL) accounts for 10 to 15% of approximately 21,450 new cases of adults with AML per year in the USA.[1] APL leukemic cells typically harbor a t (15:17) chromosomal translocation resulting in the expression of the promyelocytic leukemia-retinoic acid receptor (*PML-RARα*) gene fusion, which blocks the normal cell differentiation processes. Clinically, the disease often presents with coagulopathy that can lead to catastrophic hemorrhage. Until recently, the standard-of-care for patients with newly diagnosed with APL involved the combination of all-trans-retinoic acid (ATRA) plus anthracycline-based chemotherapy for induction and consolidation.[2] In general, patients receive two to three cycles until complete molecular remission is achieved. After consolidation, patients receive ATRA with or without low-dose chemotherapy for 1 to 2 years for maintenance.

Arsenic has been used to treat a variety of diseases such as the plague and malaria for more than 2 millennia.[3] In the late 1900s arsenic was found to have anti-leukemic activity and was used for ~70 years to treat various leukemias. In the 1990s, three teams of Chinese researchers found that intravenous (IV) arsenic trioxide (ATO) was effective in patients with APL, with complete responses (CR)

Correspondence:

FARHAD RAVANDI
fravandi@mdanderson.org

Received: June 13, 2019.

Accepted: September 24, 2019.

Pre-published: September 26, 2019.

doi:10.3324/haematol.2019.229583

Check the online version for the most updated information on this article, online supplements, and information on authorship & disclosures: www.haematologica.org/content/106/6/1567

observed in 66% of patients in one study.[4] In other studies, up to 90% of relapsed patients with APL and over 70% of newly diagnosed patients achieved responses.[5,6] Following this success, several clinical studies conducted in the USA established the safety and efficacy of IV ATO in patients with APL who had relapsed after prior ATRA + anthracycline therapy. In the first pilot study, 92% of the 12 patients treated achieved a CR with IV ATO alone, and 67% had undetectable PML-RAR transcripts.[7] In a larger trial (n=40), 85% of patients with relapsed APL achieved CR; more than three-quarters of the patients were alive after 2 years.[8] This trial formed the basis for the approval of IV ATO, Trisenox®, in the USA in 2000 and in Europe in 2002 for second line therapy of patients with APL who are refractory to - or have relapsed from - ATRA + anthracycline chemotherapy.[9] Since 2000, ATO has been used as the standard-of-care for relapsed APL, with remission rates greater than 80% as a single agent after two 25-day cycles.

Several investigators have examined the role of IV ATO in frontline therapy of patients with newly diagnosed APL and have demonstrated that this approach is feasible.[10-13] Recently, two large randomized trials have shown that the combination of ATRA and IV ATO for induction is superior to ATRA + chemotherapy in the treatment of APL patients with standard-risk disease.[14,15] Moreover, long-term follow-up of these patients showed that patients treated with ATRA + IV ATO had a significantly higher event-free and overall survival and a significantly lower cumulative relapse rate compared with the ATRA + chemotherapy cohort.[16] These findings have led to new recommendations for the use of IV ATO as a first-line therapy in combination with ATRA for the management of patients with standard-risk APL (white blood cell [WBC] count ≤10×10^9/L), with additional chemotherapy reserved for patients with high-risk disease (WBC count >10×10^9/L).[17,18] The combination of IV ATO + ATRA is also safe and effective in patients who are not suitable candidates for anthracycline-based chemotherapy, such as those with significant cardiac disease or older adults.[14,15]

As a front-line therapy for APL, ATO needs to be administered IV daily for over 100 doses, which is inconvenient, costly, and leads to a decreased quality of life for the patients. Therefore, the introduction of an oral ATO formulation could improve patients' quality of life, and drug compliance, while reducing costs.

Two oral formulations of ATO have been developed in Hong Kong. One is a liquid formulation of As_2O_3 at 1 mg/mL (pH 7.2), which was found to be highly bioavailable.[19] In relapsed APL patients, the formulation was highly active, showing an efficacy comparable to IV ATO.[20] As a maintenance regimen in APL patients with first complete remission, the formulation was effective in the long term, with a 3-year leukemia-free-survival, event-free survival, and overall-survival of 87.7%, 83.7%, and 90.6%, respectively.[21] Oral ATO incorporation into frontline treatment with ATRA and chemotherapy in newly diagnosed APL is safe and reduces relapses.[22] This oral liquid formulation did not induce QT prolongation or cardiac arrhythmias,[20,21,23] and the severity and incidence of other side effects (leucocytosis, LFT abnormalities, and skin rashes) was comparable to that of IV ATO.[20]

However, commercializing a liquid oral formulation intended to be self-administered by patients could represent a safety challenge in handling and dosing. Therefore, a solid oral formulation of ATO is preferable. The other oral formulation developed in China is a pill termed RIF containing Realgar, a naturally occurring mixture containing tetra arsenic tetra sulfide (As4S4; 30 mg per pill), *Indigo naturalis*, *Radix salvia miltiorrhizae*, and *Radix pseudostellariae*.[24] In a phase 2 clinical trial conducted in China, the formulation demonstrated a CR rate of 96.7% and a reasonable safety profile in newly diagnosed APL patients.[25] In a phase 3 study, RIF + ATRA was not inferior to IV ATO + ATRA as first-line treatment for APL, and adverse events (AE) were similar in the two arms.[26] RIF has been commercialized and is available in China.

However, these oral ATO formulations are not available in Western markets. Therefore, a unique oral powder capsule formulation of ATO, ORH-2014, was developed, for the treatment of APL and other hematologic malignancies. Herein we report the results of the first-in-human study with ORH-2014 in subjects with relapsed advanced hematological disorders. ORH-2014 safety profile, recommended dose, pharmacokinetic profile, and preliminary efficacy data are reported and discussed.

Methods

For ORH-2014 formulation development and physical properties, see the *Online Supplementary Materials and Methods.*

We conducted a multicenter phase 1 open-label, dose-escalating study to evaluate the safety, tolerability, pharmacokinetics and to determine the recommended dose and preliminary efficacy of oral ORH-2014 in patients with advanced hematologic malignancies. ORH-2014 dose-escalation was designed as 5-mg increments starting from 5 mg and could potentially go up to 50 mg, in a standard 3x3 dose-escalation scheme (described below). The starting dose (5 mg) was chosen to be approximately half of the IV ATO approved dose of 0.15 mg/kg for a 70-kg person (i.e. 5.25 mg). ORH-2014 was administered orally once daily (QD) in the fasted state. Dose-escalation was to be stopped when the mean area under the concentration-time curve from 0 to 24 hours (AUC0-24) and/or the maximum observed concentration (C_{max}) of total arsenic in plasma at a given dose of ORH-2014 was ≥30% higher than that for IV ATO at the approved dose or if the maximum tolerated dose (MTD) was reached. Anticancer agents other than ORH-2014 (including systemic chemotherapy, radiation therapy, or biologic response modifiers) were not permitted during the study, except for the temporary use of hydroxyurea. Supportive care was allowed, including antibiotics, IV electrolytes, platelet transfusions, and steroids.

Male and non-pregnant female subjects ≥18 years of age with the following advanced hematological disorders and no available therapies were eligible for enrolment: (i) Relapsed or refractory AML with nucleophosmin-1 (*NPM1*) mutations; (ii) relapsed or refractory APL; (iii) relapsed or refractory intermediate or high-risk myelodysplastic syndrome (MDS); (iv) relapsed or refractory chronic myelomonocytic leukemia (CMML) and other MDS/myeloproliferative neoplasm (MPN) overlapping syndromes; or (v) relapsed or refractory mantle cell lymphoma (MCL). Subjects were excluded if they had an Eastern Cooperative Oncology Group performance status >3; absolute myeloblast count ≥20,000/mm^3; remaining toxicities (>grade I) due to previous chemotherapy; abnormal liver function tests (above specified limits); impaired cardiac function; or had received any antineoplastic therapy (except hydroxyurea) within <5 half-lives before ORH-2014 administration. All participants gave written informed consent before entering the study.

First, a cohort of three subjects received ORH-2014 at the dose 5 mg QD, and dose-limiting toxicities (DLT) were observed for four weeks (DLT definition in the *Online Supplementary Materials and Methods*). If none of the three subjects exhibited a DLT in the four-week period, then the study could advance to the next higher dose level. At any dose level, if 1 of 3 subjects exhibited a DLT, the cohort was to be expanded to six subjects. If 1 of 6 subjects exhibited a DLT, the next subject was to be enrolled at the next higher dose level. If ≥1 of 3 or 6 subjects exhibited a DLT, then the dose level below was considered the maximum tolerated dose (MTD). Subjects with no DLT continued to receive ORH-2014 at the same dose for an additional eight weeks, followed by bone marrow evaluation to analyze response. Subjects achieving CR or partial remission (PR) at the end of the 12-week treatment period were eligible to receive an additional 12 weeks of therapy. The study was approved by the institutional review board affiliated with each study site.

Results

ORH-2014 physical properties

ORH-2014 molecular formula is AS_2O_3, As_4O_6 in form (Figure 1), and its relative molecular mass is 197.8 g/mol. ORH-2014 oral capsule formulation was developed by a lyophilization process (see the *Online Supplementary Materials and Methods*), which significantly reduces the ATO particle size and increases the particle surface area (Table 1). The aggregate particle size of the Lyopremix (see the *Online Supplementary Materials and Methods*) was about 5-10-fold smaller than that of the unprocessed ATO. The specific surface area of the Lyopremix was also significantly higher than that of the unprocessed ATO. Figure 2A shows the structure of ORH-2014 Lyopremix, which consists of a matrix of sodium lauryl sulfate with microscopic ATO crystals with well-defined morphology. The small particle size and the large surface area of the ATO Lyopremix in ORH-2014 allows rapid drug dissolution in the simulated gastric media of 0.1 N HCl (80% of the compound dissolved in 10 minutes; Figure 2B), potentially enhancing oral bioavailability.

Patient characteristics

The trial enrolled 12 patients (eight males; four females) with advanced hematologic malignancies: six with advanced MDS, four with refractory AML with NPM1

Table 1. ORH-2014 particle size and surface area.

	Unprocessed ATO	Lyophilized ATO (ORH-2014)*
Particle size (D90)	139 μm	~16-30 μm
Particle surface area	0.05 m^2/g	~2-8 m^2/g

*Range of values for nine batches of Lyopremix. See *Online Supplementary Materials* and Methods for ORH-2014 physical properties assessment. ATO: arsenic trioxide.

Table 2. Subjects' demographic and baseline characteristics.

	5 mg n=3	10 mg n=6	15 mg n=3	All subjects n=12
Age, years				
Mean (SD)	67.0 (19.1)	73.0 (9.6)	66.0 (16.1)	69.8 (12.9)
Median (min, max)	78.0 (45, 78)	76.5 (55, 81)	71.0 (48, 79)	76.5 (45, 81)
Sex, n (%)				
Female	1 (33.3%)	1 (16.7%)	2 (66.7%)	4 (33.3%)
Male	2 (66.7%)	5 (83.3%)	1 (33.3%)	8 (66.7%)
Race, n (%)				
White	3 (100%)	5 (83.3%)	2 (66.7%)	10 (83.3%)
Black/African American	–	–	1 (33.3%)	1 (8.3%)
Asian	–	1 (16.7%)	–	1 (8.3%)
All other*	–	–	–	–
Ethnicity, n (%)				
Hispanic/Latino	2 (66.7%)	–	–	2 (16.7%)
Not Hispanic/Latino	1 (33.3%)	6 (100%)	3 (100%)	10 (83.3%)
Weight, kg				
Mean (SD)	87.50 (15.43)	72.83 (12.59)	88.43 (6.25)	80.40 (13.60)
Median (min, max)	84.80 (73.6, 104.1)	73.95 (56.0, 91.0)	86.60 (83.3, 95.4)	81.50 (56.0, 104.1)
Type of hematologic malignancy				
AML	1 (33.3%)	3 (50.0%)	0	4 (33.3%)
APL	0	0	0	0
MDS	2 (66.7%)	3 (50.0%)	1 (33.3%)	6 (50.0%)
CMML/MPN	0	0	2 (66.7%)	2 (16.7%)
MCL	0	0	0	0

* All other races included Native Hawaiian or Pacific Islander, American Indian or Alaska Native, and other. AML: acute myeloid leukemia; APL: acute promyelocytic leukemia; MDS: myelodysplastic syndrome; CMML: chronic myelomonocytic leukemia; MPN: MDS/myeloproliferative neoplasm; MCL: mantle cell lymphoma.

Table 3. Common drug-related adverse events (observed in ≥2 subjects).

	5 mg n=3	10 mg n=6	15 mg n=3	All subjects n=12
Number of subjects with ≥1 drug-related AE	2 (66.7%)	4 (66.7%)	4 (66.7%)	8 (66.7%)
Nausea	2	2	1	5 (41.6%)
Diarrhea	1	1	2	4 (33.3%)
Headache	1	1	1	3 (25.0%)
Dizziness	0	1	1	2 (16.6%)
Anorexia	0	1	1	2 (16.6%)

Data are n (%) of subjects.

mutation, and two with CMML (Table 2). The median patient age was 76.5 years (range: 45-81), (83.3%) were white, the median weight was 81.5 kg (range: 56.0-104.1) and patients had a median of two prior therapies (range: 1-5).

ORH-2014 safety profile

All 12 patients were included in the safety analysis set. No DLT was reported during the four-week DLT observation period. Eight subjects (66.7%) had drug-related AE; the incidence of AE was identical in the three dose groups (66.3%) (Table 3). The most common drug-related AE were nausea (n=5), diarrhea (n=4), and headache (n=3). All but one drug-related AE were mild or moderate (grade I-II). Grade III AE of QTcF prolongation occurred in one subject (8.3%) outside of the DLT observation period (on day 68), and was attributed to ORH-2014 and concomitant levofloxacine (Levaquin®; a fluoroquinolone antibiotic). Since both levofloxacin and ATO are known to induce QT prolongation,[9,30] both were stopped. The AE resolved, and treatment with ORH-2014 alone was resumed at the same dose (5 mg), without any further occurrence of QT prolongation. The patient was able to receive ORH-2014 at 5 mg QD for a total of 171 days. There were very few renal, hepatic, and hematologic AE related to the underlying disease state, with the exception of grade I transaminitis attributed to ORH-2014; this event resolved on its own without treatment interruption or any medications. Two deaths occurred (on days 35 and 40 post dose) due to progression of the disease, both unrelated to ORH-2014.

ORH-2014 pharmacokinetic profile

Total plasma arsenic

Following single and repeated oral administration of 5, 10 or 15 mg of ORH-2014 QD, the median Tmax for total plasma arsenic occurred between 1 and 12 hours (Table 4). On day 15, C_{max} and AUC0-24 geometric means increased by 3.4- and 2.9-fold, respectively, over the 3-fold dose increase (5-15 mg), indicating that systemic exposure was nearly dose-proportional (Figure 3). There was a low correlation (below 0.2) between total the arsenic exposure and patients' BMI, suggesting that a flat dose of ORH-2014 (rather than mg/kg dose) is adequate.

On days 15 and 22, between-subject variability (geometric % CV) was generally moderate with % CV ranging from 17% to 37% for C_{max}, and from 34% to 41% for AUC0-24 (Table 4)

The mean extent of accumulation (AR, which is based on AUC0-24) was approximately 3- to 4-fold on Day 5, 4- to 5-fold (excluding a patient receiving 5 mg ORH-2014 who had a 7-fold accumulation) on Day 15, and 4- to 5-fold on Day 22 (Table 4). The approximately 5-fold accumulation indicated an effective half-life of three days. Visual inspection of trough total arsenic concentrations also indicated that a steady-state reached by day 15 (Figure 3). The observed time to reach steady-state (15 days) is consistent with an effective half-life of three days, since 97% of steady-state is achieved after five half-lives (5x3 days = 15 days).

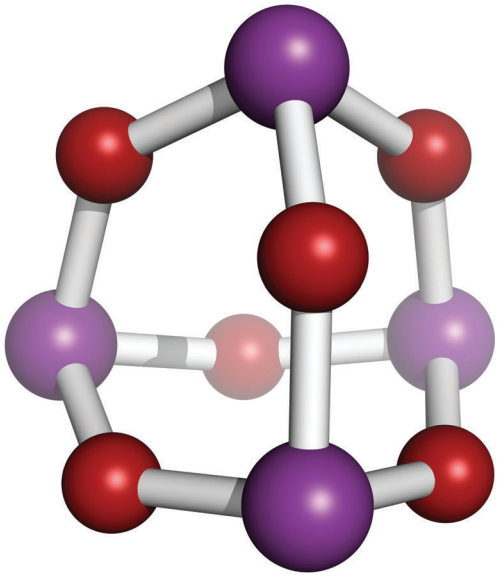

Figure 1. Arsenic oxide structural formula. Atoms are represented as spheres, with oxygen in red and arsenic in purple.

ORH-2014 at the 15 mg dose is comparable to the IV ATO approved dose (0.15 mg/kg) for adult patients. Exposure to 15 mg ORH-2014 was compared to exposure to IV ATO at the approved dose, using IV ATO historical data (Table 4). After daily administration of 10 mg ORH-2014 for 15 days, ORH-2014 C_{max} was about half of IV-ATO C_{max} at day 8 (mean: 66 *vs.* 124 ng/mL, respectively) but its AUC0-24 was similar (1,340 *vs.* 1,302 h*ng/mL, respectively). At 15 mg, ORH-2014's C_{max} was similar to IV-ATO's (mean: 114 *vs.* 124 ng/mL, respectively) but its AUC0-24 was higher (2,140 vs. 1,302 h*ng/mL).

Pharmacokinteics of arsenical species

The pharmacokinetic (PK) of arsenical species ([AsIII], [AsV], [MMAV], [DMAV]) was determined for all subjects in this study (see the *Online Supplementary Materials and*

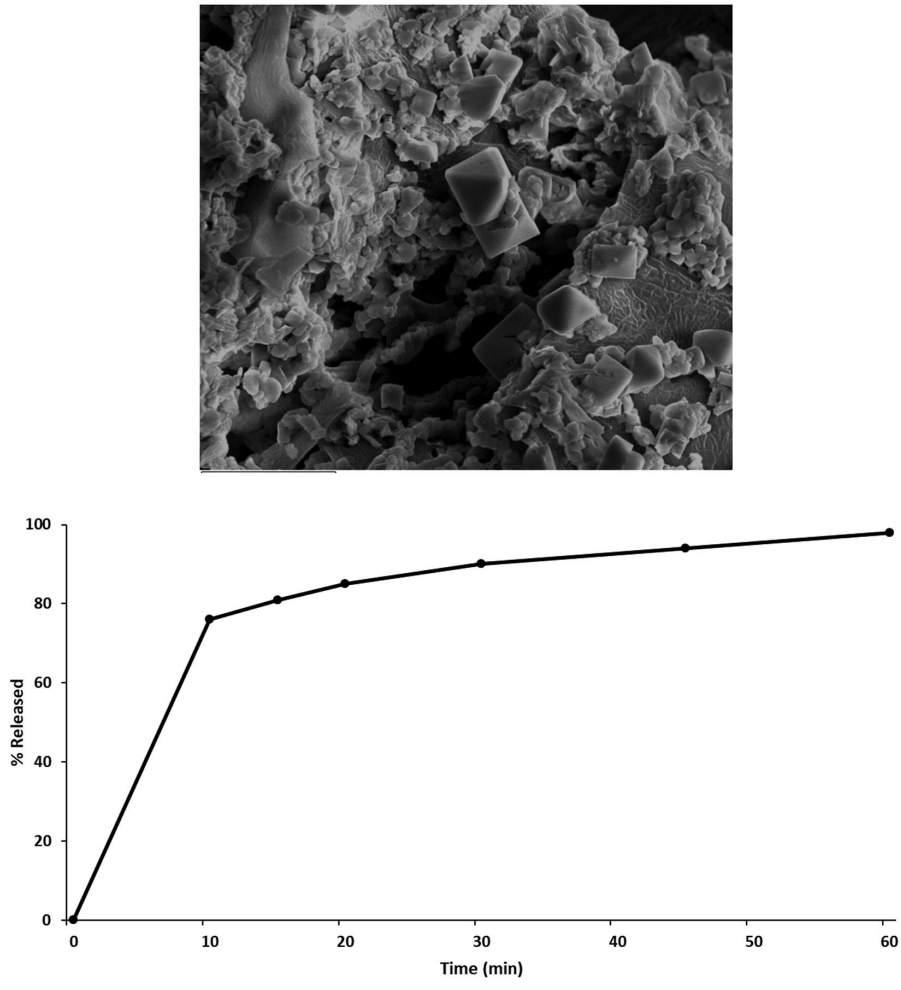

Figure 2. ORH-2014 particles and dissolution profile. A: ORH-2014 Lyopremix by scanning electron microscopy; bar represents 5 µm. B: ORH-2014 capsule dissolution kinetic. See the *Online Supplementary Materials and Methods* for ORH-2014 particle size and dissolution assessments.

Methods). Peak plasma concentrations of AsIII, the primary active species, were reached at approximately two hours across all doses (range: 1-4 hours). Plasma concentration of AsIII declined in a biphasic manner with a mean elimination half-life of 7 to 16 hours and is characterized by an initial rapid distribution phase followed by a slower terminal elimination phase. Twenty-two days after daily administration of ORH-2014 at 15 mg, AsIII C_{max} was 25 ng/mL (42% CV) and AUC was 354 ng*hr/mL (47% CV), which is comparable to the AUC of Trisenox (332 ng*hr/mL; n=6; on Day 25).[9] After administration at 5, 10 or 15 mg on a daily regimen, accumulation of AsIII ranged from 1.05 to 1.44 compared to a single dose. The primary pentavalent metabolites, MMAV and DMAV, were slow to appear in plasma (approximately 4 to 24 hours after first administration of ORH-2014), but, due to their apparent longer half-life, accumulate more upon multiple dosing than does AsIII. The extent of accumulation of these metabolites is dependent on the dosing regimen. Accumulation ranged from 1.4- to 11-fold following multiple dosing as compared to single dose administration. AsV is present in plasma only at relatively low levels. ORH-2014 AUC of As_3 species, is comparable to the AsIII AUC of IV ATO.[9]

Efficacy

Although this phase 1 study was not intended to formally determine efficacy of ORH-2014, disease improvements were observed in two patients with advanced MDS. One patient had complete marrow remission observed approximately 12 and 27 weeks after starting ORH-2014. The patient took 171 doses and was on the study for 187 days of ORH-2014 at 5 mg daily. Another patient had improvement in peripheral counts and became eligible for bone marrow transplant after 110 days of ORH-2014 dosing at 15 mg daily (this patient did not have any bone marrow procedures performed beyond the 30-day timepoint, to avoid an invasive procedure).

Discussion

In the past 5 years, the standard-of-care for non-high-risk APL patients has shifted from the combination of ATRA plus anthracycline chemotherapy to the combination of IV ATO plus ATRA, triggering new treatment guidelines.[2] However, IV ATO plus ATRA treatment regimen consists of daily IV administration of ATO for over 100 days, which represents an important burden to patients and caregivers, and can be associated with low treatment compliance, low quality of life, and high costs. Poor compliance is an important issue with IV ATO treatment due to the burden of attending lengthy daily clinic visits for months, particularly for patients who live far from the treatment center, who work, and/or have family obligations, which is common in relatively younger AML

Table 4. Pharmokinetic parameters for total arsenic.

	ORH-2014 5 mg**		ORH-2014 10 mg			ORH-2014 15 mg			IV ATO 0.15 mg/kg
	Day 1 (n=3)	Day 15 (n=3)	Day 1 (n=6)	Day 15 (n=5)	Day 22 (n=2)	Day 1 (n=3)	Day 15 (n=3)	Day 22 (n=3)	Day 8
C_{max}, ng/mL	7.22	34.0	19.9	65.6	109	24.5	114	111	**124**
	(9.5)	(16.9)	(36.8)	(37.2)	(37.0)	(39.6)	(21.1)	(29.5)	**(60)**
AUC_{0-24}, ng•h/mL	125	729	329	1340	2210	454	2140	2240	**1302**
	(1.3)‡	(21.9)	(32.7)	(37.6)	(41.2)	(36.1)	(35.8)	(40.4)	**(30)**
T_{max}, h†	12.00	8.10	2.13	2.02	1.02	3.85	1.00	1.00	–
	[12.0, 24.0]	[4.0, 8.18]	[2.00, 24.3]	[1.00, 8.08]	[0.97, 1.07]	[0.98, 24.0]	[0.90, 1.13]	[0.00, 1.95]	
RA	NA	5.14	NA	4.19	5.27	NA	4.72	4.92	**(5.5)**
		(1.4)‡		(20.7)	(40.3)		(5.9)		–

See the *Online Supplementary Materials and Methods* for PK sampling and data analyses. Geometric mean (%CV) data are presented, unless otherwise noted. *Bolded cells are historical values for IV ATO (Trisenox®) calculated from data in NDA #21-248. ** protocol was amended to add a day 22 after the second dose cohort. †Median [min, max]. ‡N = 2. C_{max}: maximum observed concentration; AUC0-24: area under the plasma drug concentration-time curve from 0 to 24 hours; T_{max}: amount of time that the drug is present at the maximum concentration in serum, RA: ratio of accumulation; NA: not analyzed.

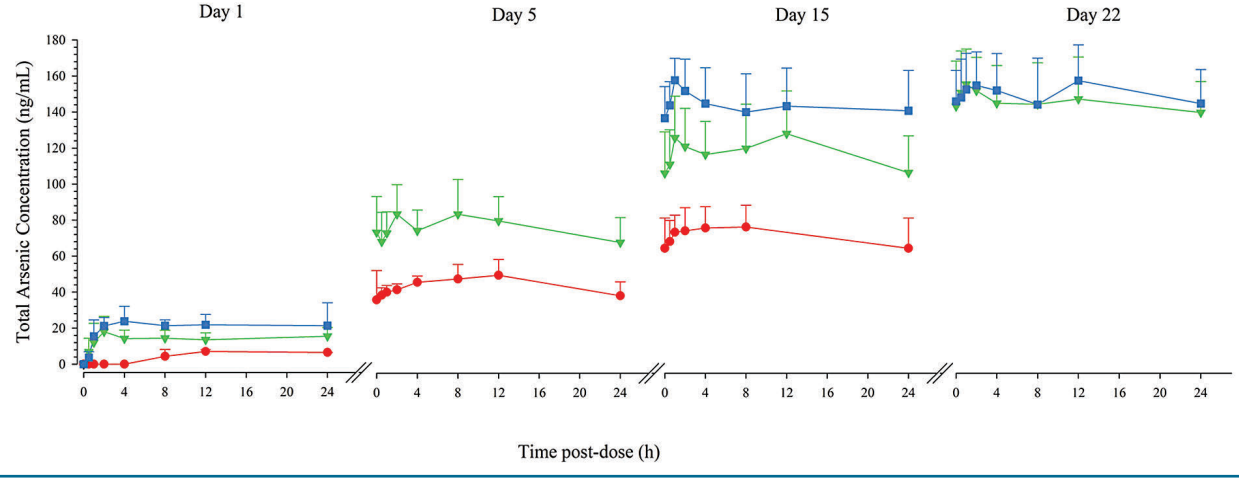

Figure 3. Plasma arsenic concentration-time curves at days 1, 5, 15, and 22. Red curves: 5 mg ORH-2014 QD (n=3); green curves: 10 mg ORH-2014 QD (n=6); blue curves: 15 mg ORH-QD (n=3). Data are arithmetic mean ± standard deviation (SD) total arsenic (ng/mL plasma). See the *Online Supplementary Materials and Methods* for pharmacokinetic (PK) data analyses. h: hours.

population. Therefore, the development and approval of an oral ATO formulation would greatly improve APL treatment by offering patients the ability to conveniently self-administer the entire treatment at home (since ATRA is also an oral drug) while carrying on their normal daily life. Oral ATO drugs are available in the Chinese market, but not approved in Western countries. To meet the need of Western countries, an oral powder capsule formulation, ORH-2014, was developed using a novel lyophilization process which results in micron-size drug particles with a large surface area that enable rapid dissolution in an acidic environment. The rapid dissolution of ORH-2014 results in a high bioavailability of arsenic, as indicated by the AUC.

ORH-2014 C_{max} and AUC for total arsenic were dose-proportional, indicating linear absorption. Treatment with ORH-2014 at 10 or 15 mg (which is equivalent to IV ATO approved dose for an adult person) resulted in an exposure (AUC0-24) similar to IV ATO at the approved dose. Correlation between total arsenic exposure and patient body weight was found to be very low (less than 0.2), implying that dose adjustment based on body mass index (BMI) (*e.g.* dosing in mg/kg) is not necessary. ORH-2014 15 mg AUC and C_{max} for As_3, the most active species, was also similar to that of IV ATO, which provides additional confidence that the 15 mg dose will be safe and potentially as effective as Trisenox. The liquid ATO formulation in Kumana *et al.* study also reported similar AUC and C_{max} than IV ATO for total arsenic.[19] ORH-2014 also resulted in small inter-patient variations in exposure, indicating reliable dosing. At 15 mg ORH-2014, administration for 25 days yielded an AUC0-24 greater than IV ATO, which fulfilled the protocol second stopping rule. (Dose-escalation was to be stopped if MTD was observed, however MTD was not reached or if ORH-2014's mean AUC0-24 and/or C_{max} was ≥30% higher as calculated in IV ATO at the approved dose). ORH-2014 and IV ATO have a similar elimination half-life of three days and 80 to 100 hours, respectively).[9]

ORH-2014 administration yielded no DLT up to a dose of 15 mg in the 12 patients with hematologic malignancies who had relapsed from prior treatments. Therefore, we recommend using the 15 mg ORH-2014 dose for future

clinical trials with ORH-2014. The most common drug-related AE (observed in ≥3 [25%] patients) were nausea, diarrhea, and headache, which were grade I-II (mild and moderate). ORH-2014 did not induce any clinically significant hepatic toxicities which are reported with IV ATO at a great frequency (16-23% and 44%, respectively).[9] Many of the adverse reactions observed with IV ATO are serious (grade ≥III): in a phase 2 study with IV ATO, 25% of patients had QTc interval ≥500 msec (grade III-IV), and the rates of grade III-IV differentiation syndrome, hyperleukocytosis, atrial dysrhythmias, and hyperglycemia were 5% to 7.5% with ORH-2014, only one drug-related AE (grade III) of QT prolongation was observed in one (8.3%) patient who was taking both ORH-2014 5 mg and fluorofloxacine, an antibiotic known to induce QT prolongation. The event was transient and reversible upon interruption of both drugs, and the patient was able to resume treatment with ORH-2014, at a 5 mg dose alone with no further cardiac conduction issues, for a total duration of 187 days on study. The fewer side effects observed with ORH-2014 could be attributed to its lower C_{max} and steadier exposure profile[3] prior to steady state (~day 15). Altogether, the findings of this phase 1 study indicate that ORH-2014 oral formulation may be safer than the approved IV ATO formulation. The convenient oral dosing could make it suitable for the treatment of APL and other hematologic malignancies at home without the need of daily hospital visits for IV administration.

Of note ORH-2014 also resulted in a lower incidence of AE, especially lower liver toxicity, compared to the other two oral arsenic formulations. Indeed, liver toxicity was observed in 48% of the patients (26% of whom had grade III-IV toxicities) with the liquid formulation,[22] and 45% (all grade I-II) with the Realgar-Indigo naturalis Formula (RIF) formulation,[26] while only one (8.3%) transient grade I liver toxicity occurred with ORH-2014, albeit this was observed in a smaller sample population (n=12).

Although this phase 1 study was not formally intended to demonstrate ORH-2014 efficacy, disease improvement was observed in one patient and another patient became eligible for bone marrow transplant with MDS. Additional studies will need to be conducted in MDS and other hematologic malignancies.

This first-in-human phase 1 study in patients with advanced hematological malignancies was intended to determine the safety profile, PK profile, and dose of ORH-2014. Therefore, in this study we did not conduct a side-by-side comparison of ORH-2014 and IV ATO, and used IV ATO historical data for comparison. A parallel comparison with IV ATO may be performed in the next planned study in patients with APL in whom IV ATO is approved. While data from a crossover design may add value to the study, it requires the drug to be held for over one week for an adequate washout of ATO, which is not acceptable in patients with advanced hematological malignancies who require ongoing treatment.

Oral formulations of ATO, including ORH-2014, could represent safer and similarly active alternatives to IV ATO and could have great utility for the treatment of patients with APL by improving the patients' quality of life and treatment compliance, while reducing the patient burden and treatment costs. Based on the findings of the present study, a flat dose of 15 mg daily ORH-2014, administered daily (like IV ATO), appears to be adequate for the induction and consolidation therapy in adult patients with hematologic malignancies in future trials. Additional studies may be conducted with alternate treatment regimen if deemed necessary. In pediatric patients, however, a per-weight dose is recommended.

Acknowledgments

The authors thank Florence Paillard for her editorial assistance, and Stuart Hossack and Mary Sherman for the expert analysis in pharmacokinetics.

References

1. NIH, National Cancer Institute; Surveillance, Epidemiology, and End Results Program (SEER). 2019 data. https://seer.cancer.gov/
2. Sanz MA, Grimwade D, Tallman MS, et al. Management of acute promyelocytic leukemia: recommendations from an expert panel on behalf of the European LeukemiaNet. Blood. 2009;113(9):1875-1891.
3. Emadi A, Gore SD. Arsenic trioxide – An old drug rediscovered. Blood Rev. 2010; 24(4-5):191-199.
4. Sun HD, Ma L, Hu XC, Zhang TD. Arsenic trioxide [Ai-lin 1] treated 32 cases of acute promyelocytic leukemia. Chin J Integrated Tradit West Med. 1992;12:170-172.
5. Shen ZX, Chen GQ, Ni JH, et al. Use of arsenic trioxide (As2O3) in the treatment of acute promyelocytic leukemia (APL): II. Clinical efficacy and pharmacokinetics in relapsed patients. Blood. 1997;89(9):3354-3360.
6. Zhang P, Wang SY, Hu XH. Arsenic trioxide treated 72 cases of acute promyelocytic leukemia. Chin J Hematol. 1996;17:58-62.
7. Soignet SL, Maslak P, Wang ZG, et al. Complete remission after treatment of acute promyelocytic leukemia with arsenic trioxide. N Engl J Med. 1998;339:1341-1348.
8. Soignet SL, Frankel SR, Douer D, et al. United States multicenter study of arsenic trioxide in relapsed acute promyelocytic leukemia. J Clin Oncol. 2001;19(18):3852-3860.
9. Trisenox® arsenic trioxide injection [Prescribing Information]. Teva Pharmaceuticals, Inc. 2000-2018. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/021248s015lbl.pdf. Accessed 13 May 2019.
10. Ravandi F, Estey E, Jones D, et al. Effective treatment of acute promyelocytic leukemia with all-trans-retinoic acid, arsenic trioxide, and gemtuzumab ozogamicin. J Clin Oncol. 2009;27(4):504-510.
11. Ghavamzadeh A, Alimoghaddam K, Rostami S, et al. Phase II study of single-agent arsenic trioxide for the front-line therapy of acute promyelocytic leukemia. J Clin Oncol. 2011;29(20):2753-2757.
12. Mathews V, George B, Lakshmi KM, et al. Single-agent arsenic trioxide in the treatment of newly diagnosed acute promyelocytic leukemia: durable remissions with minimal toxicity. Blood. 2006;107(7):2627-2632.
13. Abaza Y, Kantarjian H, Garcia-Manero G, et al. Long-term outcome of acute promyelocytic leukemia treated with all-trans-retinoic acid, arsenic trioxide, and gemtuzumab. Blood. 2017;129(10):1275-1283.
14. Lo-Coco F, Avvisati G, Vignetti M, et al. Retinoic acid and arsenic trioxide for acute promyelocytic leukemia. N Engl J Med. 2013;369(2):111-121.
15. Burnett AK, Russell NH, Hills RK, et al.; UK National Cancer Research Institute Acute Myeloid Leukaemia Working Group. Arsenic trioxide and all-trans retinoic acid treatment for acute promyelocytic leukaemia in all risk groups (AML17): results of a randomised, controlled, phase 3 trial. Lancet Oncol. 2015;16(13):1295-1305.
16. Platzbecker U, Avvisati G, Cicconi L, et al. Improved outcomes with retinoic acid and arsenic trioxide compared with retinoic acid and chemotherapy in non-high-risk acute promyelocytic leukemia: final results of the randomized Italian-German APL0406 trial. J Clin Oncol. 2017;35(6):605-612.
17. Iland HJ, Wei A, Seymour JF. Have all-trans retinoic acid and arsenic trioxide replaced all-trans retinoic acid and anthracyclines in APL as standard of care. Best Pract Res Clin

Haematol. 2014;27(1):39-52.
18. Sanz MA, Fenaux P, Tallman MS, et al. Management of acute promyelocytic leukemia: updated recommendations from an expert panel of the European LeukemiaNet. Blood. 2019;133(15):1630-1643.
19. Kumana CR, Au WY, Lee NS, et al. Systemic availability of arsenic from oral arsenic-trioxide used to treat patients with hematological malignancies. Eur J Clin Pharmacol. 2002;58(8):521-526.
20. Au WY, Kumana CR, Kou M, et al. Oral arsenic trioxide in the treatment of relapsed acute promyelocytic leukemia. Blood. 2003;102(1):407-408.
21. Au WY, Kumana CR, Lee HK, et al. Oral arsenic trioxide-based maintenance regimens for first complete remission of acute promyelocytic leukemia: a 10-year follow-up study. Blood. 2011;118(25):6535-6543.
22. Gill H, Yim R, Lee HKK, et al. Long-term outcome of relapsed acute promyelocytic leukemia treated with oral arsenic trioxide-based reinduction and maintenance regimens: A 15-year prospective study. Cancer. 2018;124(11):2316-2326.
23. Siu CW, Au WY, Yung C, et al. Effects of oral arsenic trioxide therapy on QT intervals in patients with acute promyelocytic leukemia: implications for long-term cardiac safety. Blood. 2006;108(1):103-106.
24. Zhu HH, Wu DP, Jin J, et al. Oral tetra-arsenic tetra-sulfide formula versus intravenous arsenic trioxide as first-line treatment of acute promyelocytic leukemia: a multicenter randomized controlled trial. J Clin Oncol. 2013;31(33):4215-4221.
25. Qian L. Phase II clinical trial of compound Huangdai tablet in newly diagnosed acute promyeocytic leukemia. Chin J Hematol. 2006;27:801-804.
26. Zhu HH, Wu DP, Du X, et al. Oral arsenic plus retinoic acid versus intravenous arsenic plus retinoic acid for non-high-risk acute promyelocytic leukaemia: a non inferiority, randomised phase 3 trial. Lancet Oncol. 2018;19(7):871-879.
27. Brunauer S, Emmett PH, Teller E. Adsorption of gases in multimolecular layers. J Am Chem Soc. 1938;60(2):309-319.
28. Cheson BD, Greenberg PL, Bennett JM, et al. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. Blood. 2006;108(2):419-425.
29. Platzbecker U, Fenaux P, Adès L, et al. Proposals for revised IWG 2018 hematological response criteria in patients with MDS included in clinical trials. Blood. 2019;133(10):1020-1030.
30. Levaquin (levofloxacin) [Prescribing Information]. Ortho-McNeil-Janssen Pharmaceuticals, Inc. 2008. https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/021721s020_020635s57_020634s52_lbl.pdf. Accessed 13 May 2019.