blood® Review Article

CME Article

The simpler, the better: oral arsenic for acute promyelocytic leukemia

Hong-Hu Zhu,[1-3,*] Jiong Hu,[4-7,*] Francesco Lo-Coco,[8] and Jie Jin[1]

[1]Department of Hematology, The First Affiliated Hospital, College of Medicine, and [2]Institute of Hematology, Zhejiang University, Zhejiang, China; [3]Zhejiang Province Key Laboratory of Hematology Oncology Diagnosis and Treatment, Hangzhou, Zhejiang, China; [4]Shanghai Institute of Hematology, [5]Department of Hematology, [6]Blood and Marrow Transplantation Center, and [7]Collaborative Innovation Center of Hematology, Rui Jin Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China; and [8]Department of Biomedicine and Prevention, University of Tor Vergata, Rome, Italy

Arsenic trioxide and all-*trans* retinoic acid have become the frontline treatments for patients with acute promyelocytic leukemia (APL). Despite the long wait for an oral arsenic drug, a commercially available agent, realgar–indigo naturalis formula (RIF), was not launched in China until 2009. Since then, over 5000 APL patients have been treated with oral RIF in China. Oral arsenic not only shows a clinical efficacy comparable to that of IV formulations but also displays a better safety profile, improved quality of life, and lower medical costs for patients. The promising results promote incorporating an outpatient postremission therapy model into clinical practice for both low-risk and high-risk APL patients in China. In this review, we discuss the evolution of oral arsenic RIF in the treatment of APL, with a special focus on how to address the related complications during induction therapy. (*Blood*. 2019;134(7):597-605)

JOINTLY ACCREDITED PROVIDER™
INTERPROFESSIONAL CONTINUING EDUCATION

Medscape Continuing Medical Education online

In support of improving patient care, this activity has been planned and implemented by Medscape, LLC and the American Society of Hematology. Medscape, LLC is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

Medscape, LLC designates this Journal-based CME activity for a maximum of 1.00 *AMA PRA Category 1 Credit(s)*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to 1.0 MOC points in the American Board of Internal Medicine's (ABIM) Maintenance of Certification (MOC) program. Participants will earn MOC points equivalent to the amount of CME credits claimed for the activity. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABIM MOC credit.

All other clinicians completing this activity will be issued a certificate of participation. To participate in this journal CME activity: (1) review the learning objectives and author disclosures; (2) study the education content; (3) take the post-test with a 75% minimum passing score and complete the evaluation at **http://www.medscape.org/journal/blood**; and (4) view/print certificate. For CME questions, see page 659.

Disclosures

Editor Bob Löwenberg served as advisor or consultant for Clear Creek Bio; served as a speaker or a member of a speakers bureau for Astellas Pharma, Inc. and Celgene Corporation; and owns stocks, stock options, or bonds from Frame Therapeutics. CME questions author Laurie Barclay, freelance writer and reviewer, Medscape, LLC and the authors declare no competing financial interests.

Learning objectives

Upon completion of this activity, participants will be able to:

1. Describe the efficacy of oral arsenic realgar -indigo naturalis formula (RIF) in the treatment of acute promyelocytic leukemia (APL)
2. Determine the toxicity of oral arsenic RIF in the treatment of APL and strategies to address associated complications during induction therapy
3. Identify clinical implications regarding use of oral arsenic RIF in the treatment of APL

Release date: August 15, 2019; Expiration date: August 15, 2020

Introduction

Acute promyelocytic leukemia (APL) has become a highly curable disease.[1-4] All-*trans* retinoic acid (ATRA) and arsenic trioxide (ATO) are the backbone of modern treatments for APL and have led to complete remission (CR) in 90% to 100% of patients in clinical trials and an overall survival (OS) between 86% and 97%.[5-15] The practice-changing study APL0406 reported by Lo-Coco et al demonstrated that non–high-risk APL patients can be cured using a chemotherapy-free ATRA and ATO combination regimen,[10,14] which provided the evidence for the National Comprehensive Cancer Network guidelines.[16]

However, patients receiving IV ATO must be admitted to the hospital, which is not cost-effective and is inconvenient. Therefore, an oral arsenic drug has been long awaited.[17-20] The only commercially available agent, named realgar–indigo naturalis formula (RIF), was launched in China in 2009. RIF not only shows a clinical efficacy but also displays a better safety profile, improved quality of life, and lower medical costs for patients.[21-23] The promising results led to the incorporation of RIF into the China APL management guidelines starting in 2014.[24,25] There is a strong need for oral arsenic for APL patients both in China and in western countries.[17-20,25-30] Although the use of oral ATO has been reviewed,[18] oral RIF, the only commercially available oral agent, has never been comprehensively reviewed. Therefore, in this review, we systematically discuss the Chinese experiences with oral RIF for the treatment of APL, with a special focus on the management of RIF-related complications.

History

In China, there are 4 types of oral arsenic formulations: tetra-arsenic tetrasulfide (As_4S_4), which is isolated from a mined ore known as realgar; ATO (As_2O_3); Qinghuang powder (realgar and indigo naturalis); and RIF (realgar, indigo naturalis, radix salviae miltiorrhizae, and radix pseudostellariae). Zhou et al first reported that 2 newly diagnosed APL patients achieved CR and maintained continuous CR over 4 years using Qinghuang powder in 1986.[31] Lu et al reported long-term follow-up data in patients treated with oral As_4S_4 in 2002.[32] Kumana et al reported on an oral ATO solution as treatment of APL patients in 2002[33]; a novel capsule formulation of ATO developed in Australia is being evaluated by the Australasian Leukaemia and Lymphoma Group (ALLG) phase 1 study (APML5; ACTRN12616001022459). ORH-2014 is another oral formulation of ATO. A phase 1 study to determine the recommended dose and evaluate the safety and tolerability of ORH-2014 in patients with advanced hematological disorders (clinicaltrials.gov identifier NCT03048344; led by F. Ravandi, MD Anderson Cancer Center, Houston, TX) was completed in February 2019. Based on its promising results, ORH-2014 will enter a phase 3 trial in the near future

However, RIF is currently the only commercially available agent. RIF was first developed by Huang et al in 1980, and the first study of RIF for APL was reported in 1988.[34] Based on the results of systematic studies by Huang et al and Qian et al, this drug was approved by the Chinese Food and Drug Administration (FDA) in 2009 for the treatment of APL.[34,35] One pill of RIF is 270 mg and contains 30 mg of realgar, 125 mg of indigo naturalis, 50 mg of radix salviae miltiorrhizae, 45 mg of radix pseudostellariae, and 20 mg of garment film. Wang et al demonstrated the anti-APL activity of RIF in vitro and in vivo.[36] They found that indigo naturalis and radix salviae miltiorrhizae facilitate intracellular arsenic transport by upregulating expression of aquaglyceroporin 9. The clear synergistic effects of different components were demonstrated on the differentiation and apoptosis of APL cells.[36] Subsequently, a series of clinical trials led by Zhu et al promoted the incorporation of RIF into the China APL management guidelines and its widespread use in China.[21-23,28-30,37-40]

In China, RIF is commercially available in all regions except for Hong Kong, Macau, and Taiwan. Over 5000 APL patients, adult and pediatric, have been treated with oral RIF. The high cost-effectiveness of RIF is also an important factor for its widespread use. The cost of RIF treatment is approximately $22.00 (US dollars; 150 ¥) per day for a patient with a body weight of ~60 kg. The median medical costs were $13 183.49 in the RIF group and $24 136.98 in the IV ATO group ($P < .0001$) in a chemotherapy-included protocol,[29] which included not only the price of the drugs but also prices of blood products, laboratory tests, non-laboratory tests, hospital bed/day care, and other medical costs. The higher medical costs mostly resulted from the related costs of daycare facilities for infusion of IV ATO.

With an entirely chemotherapy-free outpatient postremission therapeutic model with oral ATRA and RIF, the median total medical costs were further decreased to $4675.00 (range, $3174.00 to $12 698.00) in non–high-risk APL patients[30] and $7540.00 ($5490.00 to $26 530.00) for high-risk patients.[36] In China, most costs (70%~85%) of RIF are covered by Basic Insurance for Urban Employees, Basic Insurance for Urban Residents, and the New Rural Cooperative Medical Scheme, which cover over 95% of the population.[28] Therefore, the direct economic burden of patients with APL is significantly reduced, which makes RIF particularly attractive in China.

Pharmacokinetic

Oral RIF resulted in gradual intestinal absorption. When administered orally at 1 dose of 2.5 g (including 0.4 g of As_4S_4) in 10 heathy donors, the results showed a maximum serum concentration (Cmax) of 0.1057 ± 0.0031 mg/L, half-life t1/2α of 3.207 ± 0.526 hours, t1/2β of 9.266 ± 1.344 hours, and area under the curve (AUC) of 2.5508 ± 0.1528 mg × h/L.[41] When administered IV, almost all the ATO bound to hemoglobin and quickly leaves the circulation to peripheral tissues. Arsenic accumulates majorly in the hair, nails, liver, lungs, heart, and kidneys. When administered at 1 dose of 10 mg of ATO in 8 APL patients, the results showed a Cmax of 6.85 μmol/L (5.54-7.30), t1/2α of 0.89 ± 0.29 hours, and t1/2β of 12.13 ± 3.31 hours.[42]

When administered orally at 60 mg/kg per day of RIF and 25 mg/m^2 per day of ATRA every day, a sustained plasma arsenic concentration will be attained after 7 days, which is less than that seen with IV ATO at 0.16 mg/kg per day (median, 24.4 μg/L [range,11.5-64.0 μg/L] and 56.3 μg/L [range, 21.7-89.5 μg/L]; $P = .0048$).[21] Both RIF and ATO were predominantly excreted by the kidney. We found that after completing12 months of therapy with RIF or ATO, the arsenic concentrations in the hair, nail, plasma, and urine samples were all in the normal range described for healthy controls.[21]

Efficacy

Huang et al performed a series of studies to confirm the efficacy of RIF for APL patients.[34,35,43-45] In the earliest study, RIF alone (n = 44) achieved a CR rate of 100% in newly diagnosed and relapsed APL patients.[34] A CR rate of 93.8% (15 of 16) was achieved when RIF plus chemotherapy was used as induction therapy.[34] In a subsequent study that included newly diagnosed (n = 161) and relapsed (n = 43) APL patients in a single center between 1988 and 2005, a CR rate of 96.08% (196 of 204) was achieved with 3-year and 5-year OS rates of 88.52% and 86.88%, respectively, when RIF was combined with chemotherapy as postremission therapy.[43] A multicenter randomized, double-blinded phase 2 trial was designed to compare the efficacy and safety of RIF vs ATRA as induction therapy.[35] The CR rates were 96.7% (59 of 61) and 94.9% (56 of 59) for the RIF and ATRA groups, respectively. The time to achieve CR was 49 days and 44 days, respectively.[35] These data promoted the approval of RIF by the Chinese FDA in 2009.

To assess the efficacy of combining RIF and ATRA as a first-line treatment, we initiated a randomized phase 3 trial of RIF vs an IV ATO formulation in 242 newly diagnosed patients with APL.[21] All patients received ATRA combined with arsenic as induction therapy and 3 cycles of consolidation chemotherapy with homoharringtonine, mitoxantrone, or daunorubicin plus cytarabine for the maintenance phase. RIF was confirmed to be noninferior to IV ATO in terms of 2-year disease-free survival (DFS; 98.1% vs 95.5%), CR rate, and OS.[21] The long-term follow-up data showed that the estimated 7-year cumulative incidence of relapse (CIR), event-free survival (EFS), and OS rates were similar between the RIF and ATO groups (4.69% vs 5.25%, $P = .98$; 93.70% vs 89.37%, $P = .37$ and 95.37% vs 90.92%, $P = .31$, respectively). The estimated 7-year CIR, EFS, and OS were also similar between the high-risk and non–high-risk groups (2.44% vs 5.04%, $P = .55$; 91.20% vs 91.49%, $P = .74$; and 93.48% vs 92.96%, $P = .82$).[22] Based on the APL0406 study reported by Lo-Coco et al with a chemotherapy-free regimen for APL,[10] we performed a pilot study in which 20 patients with non–high-risk APL were enrolled, and a CR rate of 100% was achieved under the treatment with RIF and ATRA without chemotherapy with a median of 29.5 days (range, 28-40 days).[30] All 20 patients were alive as of 1 February 2019 and were in CR with a median follow-up of 65 months (range, 59-71 months). An outpatient postremission treatment significantly decreased the health care–related costs.[26,30] Subsequently, we initiated a randomized controlled trial to compare the efficacy and toxicity of RIF-ATRA with IV ATO-ATRA in patients with newly diagnosed non–high-risk APL.[23] In total, 109 patients were enrolled and assigned to the RIF-ATRA (n = 72) or ATO-ATRA (n = 37) treatment groups. After a median follow-up of 32 months, the 2-year EFS was 97% patients (67 of 69) in the RIF-ATRA group and 94% (34 of 36) in the ATO-ATRA group in the modified intention-to-treat population. Noninferiority was confirmed in both the intention-to-treat population and the per-protocol population. During induction therapy, 2 patients in the ATO-ATRA group died of hemorrhage.[23]

The high-risk APL patients are at the center of the last battle for a cure for all APL patients.[13,37,46] We conducted a single-center cohort study in 20 high-risk APL patients to evaluate the efficacy and safety of RIF plus ATRA between April 2014 and September 2016.[37] RIF (60 mg/kg per day) plus ATRA (25 mg/m^2 per day) was combined as induction therapy until CR. Hydroxyurea alone or combined with cytarabine was used to control the hyperleukocytosis during induction therapy. The consolidation therapy included RIF in a 4-week-on and 4-week-off regimen for 4 cycles and ATRA in a 2-week-on and 2-week-off regimen for 7 cycles. All 20 patients achieved CR with a median time of 30 days (range, 28-50 days). With a median follow-up of 33 months, no hematological relapse occurred. Only 2 patients had a molecular relapse at 12 and 15 months. The estimated 3-year OS and EFS rates are 100% and 89.4%, respectively.[33] This outpatient postremission treatment proved to be effective, convenient, and cost-saving for high-risk APL.

For pediatric patients with APL, an oral chemotherapy-free outpatient model is also appealing. We conducted a single-center cohort study between April 2014 and October 2016. Nine patients (13~18 years old) received the same protocol as that in previous reports.[46] With a median follow-up of 15 months, all of the 9 patients achieved hematologic CR and complete molecular remission. The overall hospitalization time was 17 days (4-37 days). No hematological or molecular relapse occurred at the last follow-up. Both the estimated 2-year EFS and OS rates were 100%. Of note, all of the patients completed the postremission therapy on an outpatient basis with good quality of life.[46] In China, a randomized trial was designed to compare between IV ATO and oral RIF in the pediatric patients.[47] Eighty-two newly diagnosed pediatric APL patients were randomly assigned to the ATO (n = 42) or RIF (n = 40) group. Induction and consolidation treatment contained ATO or RIF, ATRA, and low-intensity chemotherapy. They found that the estimated 5-year EFS rate was 100% in both groups, and the adverse events were mild. However, patients in the RIF group had significantly shorter hospital stays than those in the ATO group. This interim analysis shows that RIF was as effective and safe as IV ATO for pediatric APL, with the advantage of reducing the length of hospital stays. A multicenter randomized controlled trial led by Chinese Children's Leukemia Group of APL (CCLG-APL) was initiated to compare RIF plus ATRA and ATO plus ATRA in a chemotherapy-free regimen and has been ongoing since July 2016 (ChiCTR-OIN-17011227).

Table 1 summarizes the recent trials using RIF or IV ATO and ATRA as frontline treatment of newly diagnosed APL. There may be several reasons for the relatively low early death rate (~1%) in the RIF group such as the bias of clinical trials mostly including low-risk patients, experienced physicians, the timely hospitalization and availability of ATRA, and RIF. A prospective registration trial aiming to define the real-world early death rates using RIF and ATRA as induction is now under way in China and we await the results.

Toxicity

Leukocytosis

Leukocytosis, defined as a white blood cell (WBC) count over 10×10^9/L, is the most common complication (>50%) during induction therapy with RIF and ATRA in non–high-risk APL patients. Recognizing the risk factors for leukocytosis and providing preemptive treatment is important in clinical practice. We evaluated the kinetics of WBCs during induction treatment with RIF and ATRA in 35 non–high-risk APL patients.[39] The median initial and peak WBC counts were 1.62 (0.61-9.89) $\times 10^9$/L and

Table 1. The recent trials including RIF or ATO plus ATRA as frontline treatment of APL patients

Reference	Type of study setting	Arsenic type	No. of patients	% high risk	Induction	HCR %	ED %	DS %	Hepatic toxicity %	Consolidation	Maintenance	MCR %	CIR %	DFS %	EFS %	OS %
Lo-Coco 2013[10]	Randomized phase 3	ATO	77	0	ATO 0.15 mg/kg/d +	100	0	19	63	ATRA 45mg/ms/d	No	100	1 (2 y)	97 (2 y)	97 (2 y)	99 (2 y)
					ATRA 45 mg/ms/d				(grade 3-4)	2 wk on/2 wk off for 7 mo						
										ATO 0.15mg/kg/d						
										4 wk on/4 wk off for 7 mo						
Zhu 2013[21]	Randomized phase 3	RIF	111	19	RIF 60 mg/kg/d +	99.1	0.9	19	64.9	Chemotherapy	ATRA 25 mg/ms/d for 2 wk/mo(in mo1)+RIF 60 mg/kg/d for 2 wk/mo(in mo 2 and mo 3) for 2 y	100	n = 1	98.1 (2 y)		99.1 (3 y)
					ATRA 25 mg/ms/d					3 cycles	RIF 60 mg/kg/d for 2 wk/mo					
											(in mo 2 and mo 3) for 2 y					
		ATO	114	21	ATO 0.16 mg/kg/d +	97.4	2.6	24.8	74.5	Chemotherapy	ATRA 25 mg/ms/d for 2 wk/mo(in mo1)+	100	n = 1	95.5 (2 y)		96.6 (3 y)
					ATRA 25 mg/ms/d					3 cycles	ATO 0.16 mg/kg/d for 2 wk/mo					
											(in mo 2 and mo 3) for 2 y					
Zhu 2014[30]	Nonrandomized	RIF	20	0	RIF 60 mg/kg/d +	100	0	10	55	ATRA 25mg/ms/d	No	100	n = 0	100		100
					ATRA 25 mg/ms/d					2 wk on/2 wk off for 7 mo				(14 mo and 4y)		(14 mo and 4 y)
										RIF 60 mg/kg/d						
										4 wk on/4 wk off for 7 mo						

6-MP, 6-mercaptopurine; DS, differentiation syndrome; ED, early death; GO: gemtuzumab ozogamicin; HCR, hematological complete remission; IDA, idarubicin; MCR, molecular remission; MTX, methotrexate; NA, not applicable; PO, postoperatively.

Table 1. (continued)

Reference	Type of study setting	Arsenic type	No. of patients	% high risk	Induction	HCR %	ED %	DS %	Hepatic toxicity %	Consolidation	Maintenance	MCR %	CIR %	DFS %	EFS %	OS %
Burnett 2015[12]	Randomized phase 3	ATO	116	26	ATO 0.3 mg/kg/days 1-5 → 0.25 mg/kg,2/wk, wk 2-8	94	4	19	71	ATRA 45mg/ms/d	No	NA	1 (4 y)	97 (4 y)	91 (4 y)	93 (4 y)
					ATRA 45 mg/ms/d +					2 wk on/2 wk off for 7 mo						
					GO in high-risk					ATO 0.25mg/kg twice weekly						
										4 wk on/4 wk off for 7 mo						
Iland 2015[13]	Nonrandomized	ATO	124	18	ATO 0.15 mg/kg/days 9-36 +	95	3	14	44	ATRA 45mg/ms/d + ATO 0.15mg/kg/d	ATRA 45 mg/m^2/days 1-14 every 90 d6-MP 50-90 mg/m^2/wk days 15-90	100		97 (5 y)	95 (5 y)	94 (5 y)
					ATRA 45 mg/ms/days 1-36 +					for 28days for 1st cycle	6-MP 50-90 mg/m^2/wk days 15-90					
					IDA 6-12 mg/ms/days 2,4,6,8					ATRA 45mg/ms/d days 1-7,15-21 and 29-35 + ATO 0.15 mg/kg/d 5 d	MTX 5-15 mg/m^2/wk PO days 15-90					
										per week for 5 wk for 2rd cycle	×8 cycles					
Abaza 2017[15]	Nonrandomized	ATO	187	28.9	ATO 0.15 mg/kg/d +	96	4	11	14	ATRA 45 mg/ms/d	No	98	4 (5 y)	96 (5 y)	85 (5 y)	88 (5 y)
					ATRA 45 mg/ms/d +				(grade 3-4)	2 wk on/2 wk off for 7 mo						
					GO in high-risk					ATO 0.15 mg/kg/d						
										4 wk on/4 wk off for 7 mo						

6-MP, 6-mercaptopurine; DS, differentiation syndrome; ED, early death; GO: gemtuzumab ozogamicin; HCR, hematological complete remission; IDA, idarubicin; MCR, molecular remission; MTX, methotrexate; NA, not applicable; PO, postoperatively.

Table 1. (continued)

Reference	Type of study setting	Arsenic type	No. of patients	% high risk	Induction	HCR %	ED %	DS %	Hepatic toxicity %	Consolidation	Maintenance	MCR %	CIR %	DFS %	EFS %	OS %
Zhu 2018[38]	Nonrandomized	RIF	20	100	RIF 60 mg/kg/d +	100	0	35	45	ATRA 25 mg/ms/d	No	100	10		89.4 (3 y)	100 (3 y)
					ATRA 25 mg/ms/d+					2 wk on/2 wk off for 7 mo						
					GO in low-dose chemo					RIF 60 mg/kg/d						
										4 wk on/4 wk off for 7 mo						
Zhu 2018[23]	Randomized phase 3	RIF	69	0	RIF 60 mg/kg/d +	100	0	26	58	ATRA 25 mg/ms/d	No	100	3 (2 y)		97 (2 y)	100 (2 y)
					ATRA 25 mg/ms/d					2 wk on/2 wk off for 7 mo						
										RIF 60 mg/kg/d						
										4 wk on/4 wk off for 7 mo						
		ATO	36	0	ATO 0.16 mg/kg/d +	94	6	28	78	ATRA 25 mg/ms/d	No	100	0 (2 y)		94 (2 y)	94 (2 y)
					ATRA 25 mg/ms/d					2 wk on/2 wk off for 7 mo						
										ATO 0.16mg/kg/d						
										4 wk on/4 wk off for 7 mo						
Yang 2018[48]	Randomized phase 3 (children)	RIF	40	20	RIF 135 mg/kg/d +	100	0	2.5	5	Chemotherapy-based	ATRA+RIF/MTX-6MP/ATRA/MTX-6MP	100	0 (5 y)		100 (5 y)	100 (5 y)
					ATRA 25 mg/ms/d +				(grade 3-4)	3 cycles	in mo 1-3 for 8 cycles (2y)					
					mitoxantrone											
		ATO	42	33.3	ATO 0.16 mg/kg/d +	100	0	9.5	2.4	Chemotherapy-based	ATRA+ATO/MTX-6MP/ATRA/MTX-6MP	100	0 (5 y)		100 (5 y)	100 (5 y)
					ATRA 25 mg/ms/d +				(grade 3-4)	3 cycles	in mo 1-3 for 8 cycles (2 y)					

6-MP, 6-mercaptopurine; DS, differentiation syndrome; ED, early death; GO: gemtuzumab ozogamicin; HCR, hematological complete remission; IDA, idarubicin; MCR, molecular remission; MTX, methotrexate; NA, not applicable; PO, postoperatively.

13.93 (2.16-80.01) × 10^9/L, respectively. Leukocytosis showed a single peak wave in all patients, and the median time to peak was 10 days (range, 2-20 days). We found a cutoff value of 5 days of WBC doubling time with a specificity of 69.23% and a sensitivity of 90.91% to predict leukocytosis. In a subsequent trial, we performed preemptive treatment to diminish the rate of leukocytosis.[23] If the WBC count was (4-10) × 10^9/L before treatment, hydroxyurea was added on the first day using a dose of 1.0 thrice daily, by mouth, days 1 to 7. If the WBC count was $<4 \times 10^9$/L before treatment, hydroxyurea (the dose of 1.0 thrice daily, by mouth, days 1-7) was added when the WBC count increased to $>4 \times 10^9$/L. When the WBC count increases to over 30×10^9/L during induction treatment, ATRA or RIF should be stopped for 3 to 7 days, and anthracyclines or cytosine arabinoside could be used. Among the RIF-ATRA group, 46 of the 69 patients (67%) received hydroxycarbamide, 15 (22%) received cytarabine, and 5 (7%) received anthracyclines during induction therapy. Leukocytosis developed in 28 of 69 patients (41%) during induction therapy with RIF and ATRA, and no early deaths occurred due to leukocytosis during induction therapy.[23]

For high-risk APL patients, the management of leukocytosis is urgent in clinical practice. In a cohort study that included 20 patients, we adopted WBC-based minimal chemotherapy to diminish the burden of leukemia.[37] For patients with a WBC count of (10-20) × 10^9/L before treatment, only hydroxyurea (3.0 g daily in an oral divided dose) was used from the first day until a WBC count $<10 \times 10^9$/L was achieved. For patients with a WBC count $>20 \times 10^9$/L before treatment, hydroxyurea (3.0 g daily) and cytarabine (200 mg daily) were used from the first day to diminish the burden of leukemia until there was a WBC count $<10 \times 10^9$/L. With this strategy, all 20 patients safely achieved CR and avoided the exacerbation of disseminated intravascular coagulation and bone marrow suppression associated with regular standard-dose chemotherapy.

Differentiation syndrome

Differentiation syndrome (DS) is a relatively common and severe complication seen in APL patients treated with ATRA and/or ATO.[48,49] DS occurs in ~10% to 25% of APL patients during induction therapy after the start of ATRA and/or ATO.[50,51] In cases of suspected DS, discontinuing the administration of ATRA and/or ATO and administering dexamethasone at a dose of 10 mg every 12 hours for a minimum of 3 days along with a diuretic is recommended. For severe DS, ATRA and/or ATO treatment should be discontinued.[52] Some clinical trials used prophylactic steroids for all patients during induction therapy to reduce the incidence and severity of DS.[53]

Among patients with WBC counts $<50 \times 10^9$/L, DS developed in 22 of 114 patients (19%) in the RIF-ATRA group and 29 of 117 patients (24.8%) in the ATO-ATRA group without prophylactic steroids.[21] In our other randomized controlled trial study that included only non–high-risk APL patients, DS developed in 26% patients (18 of 69) in the RIF-ATRA group and in 28% patients (10 of 36) in the ATO-ATRA group.[23] The median time of DS occurrence was 8 days in the RIF-ATRA group and 6 days in the arsenic trioxide–ATRA group. Severe DS occurred in 2 of 69 patients (3%) in the RIF-ATRA group and 1 of 36 patients (3%) in the arsenic trioxide–ATRA group and was fatal in 1 patient assigned to the ATO-ATRA group.[23] When using prophylaxis prednisone to treat DS in the APL0406 study, the rate of DS was relatively low.[10] DS developed in 19% of the ATO-ATRA group and in 16% of the ATRA-chemotherapy group. Severe DS rate was 6% in each group and was fatal in 2 patients in the ATRA-chemotherapy group. Until now, there has been no prospective randomized trial to answer whether prophylaxis approach decreases the incidence and mortality of DS. In patients with severe DS, temporary cessation of ATRA and/or ATO is recommended.[52,53] Both drugs may be restarted once the syndrome has resolved.

Liver damage

Hepatotoxicity has frequently been reported in studies using arsenic with or without ATRA, especially in terms of an increase in liver enzymes. This complication may occur in up to 60% of cases.[10] However, hepatotoxicity is generally reversible and can be successfully managed with a decrease or the temporary discontinuation of arsenic and/or ATRA. No fatal hepatic failure has been reported in recent trials.[10,12]

RIF, as a first-line monotherapy in a single-center study, reported hepatotoxicity in 16 of 204 patients (7.8%), including 161 newly diagnosed and 43 relapsed APL patients.[43] In a multicenter RCT study, RIF induction monotherapy led to hepatotoxicity in 8 of 78 newly diagnosed APL patients (10%).[35]

After combining RIF with ATRA, the rate of hepatotoxicity increases significantly compared with that of RIF or ATRA alone, although the rate of grade 3-4 toxicity is relatively low. In our RCT study that included APL patients with WBC counts $<50 \times 10^9$/L, hepatotoxicity occurred in 74 of 114 patients (64.9%) and 87 of 117 patients (74.5%) in the RIF-ATRA group and ATO-ATRA group, respectively.[21] The rate of grade 3-4 liver toxicity was 9.6% and 12.0%, respectively. The incidence of grade 1-2 liver toxicity was 62.5% and 55.3%. All patients were treated primarily with a temporary (<2-week duration) dose reduction or discontinuation, and when the symptoms/signs dissipated, all patients were able to resume the treatment regimen without dose deescalation. In another RCT study we conducted, including non–high-risk APL,[23] grade 1-4 hepatic toxicity was 58% (40 of 69) in the RIF-ATRA group and 78% (28 of 36) in the ATO-ATRA group (Table 3 in Zhu et al[23]) and grade 3-4 hepatic toxicity was 9% vs 14%. The toxicity was resolved with the temporary discontinuation of ATRA, arsenic, or both. In contrast, the rate of hepatotoxicity was relatively low in our recent study of 20 high-risk APL patients.[37] Nine of 20 patients (45%) in the RIF-ATRA group had grade 1-2 hepatotoxicity, and no grade 3-4 hepatotoxicity occurred.

Diarrhea

With the use of RIF as a monotherapy first-line treatment in a single-center study, diarrhea occurred in 31 of 204 patients (15%), including 161 newly diagnosed and 43 relapsed APL patients.[43] In a multicenter RCT study, RIF as induction monotherapy led to diarrhea in 6 of 78 newly diagnosed APL patients (7.7%).[35] After combining RIF with ATRA in non–high-risk APL patients, 6 of 66 patients(9%) in the RIF-ATRA group and 2 of 36 patients (6%) in the ATO-ATRA group had diarrhea.[23]

Prolongation of the QTc interval

Prolongation of the QTc interval on electrocardiography (ECG) is a common and well-documented side effect of ATO. The

GIMEMA-SAL-AMLSG APL0406 trial reported prolonged QTc intervals in 15 patients in the ATRA-ATO group (16%).[10]

A prolonged QTc interval is not a common side effect of RIF at dose of 60 mg/kg per day. However, at a high dose of 7.5 g per day as a monotherapy first-line treatment in a single-center study, prolonged QTc intervals (≥440 ms) occurred in 17 of 71 newly diagnosed APL patients (23.9%).[42] Moreover, clinically significant arrhythmias are very rare, and none were reported in the most recent trials using RIF and ATRA as first-line therapy.[21,23,30] Because overt electrolyte depletion during RIF and ATRA induction therapy is rare, K^+ and Mg^{2+} replacement is not routinely recommended during home-based therapy. ECG monitoring of QTc prolongation is recommended at least once at each cycle of RIF.

Conclusions and future directions

Arsenic, as an ancient drug, has recently been revised to cure newly diagnosed and relapsed APL, both as a single agent and in combination with other agents. We and others have observed that an oral arsenic RIF had equal activity to and possibly a more favorable toxicity profile than IV ATO, with superior patient quality of life and lower costs. The combination of RIF and ATRA has become the first-line treatment of newly diagnosed APL patients in China. Other derivatives of arsenic may also be active in the clinical setting. An entirely oral, chemotherapy-free, outpatient-based postremission treatment has become a reality for both low-risk APL patients, with studies that showed sufficient evidence, and for high-risk patients, with studies that showed promising primary results. The results of ongoing trials, including one in South America advocated by the International Consortium on Acute Leukemia of the American Society of Hematology (ASH-ICAL; which seeks to confirm the success of oral RIF), are eagerly awaited. On the road to curing APL, the best summary is: the simpler, the better.

Acknowledgments

This work was supported by grants from the National Natural Science Foundation of China (81570128 and 81820108004) and the National Key R&D Program of China (2016YFE0202800).

The authors dedicate this article to Francesco Lo-Coco, in acknowledgment of his continuous generous support of these studies on oral arsenic for APL.

Authorship

Contribution: H.-H.Z., J.H., and J.J. drafted the manuscript and contributed to the final draft; and F.L.-C. provided suggestions and comments about the manuscript.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

Francesco Lo-Coco died on 3 March 2019.

ORCID profiles: H.-H.Z., 0000-0003-2343-0436; J.J., 0000-0002-8166-9915.

Correspondence: Hong-Hu Zhu, Department of Hematology, The First Affiliated Hospital, College of Medicine, Zhejiang University, #79 Qingchun Rd, Hangzhou, 310003, People's Republic of China; e-mail: zhuhhdoc@163.com; or Jie Jin, Department of Hematology, The First Affiliated Hospital, College of Medicine, Zhejiang University, #79 Qingchun Rd, Hangzhou, 310003, People's Republic of China; e-mail: jiej0503@zju.edu.cn.

Footnotes

Submitted 24 March 2019; accepted 29 April 2019. Prepublished online as *Blood* First Edition paper, 21 May 2019; DOI 10.1182/blood.2019000760.

*H.-H.Z. and J.H. contributed equally to this review.

The online version of this article contains a data supplement.

REFERENCES

1. Wang ZY, Chen Z. Acute promyelocytic leukemia: from highly fatal to highly curable. *Blood*. 2008;111(5):2505-2515.
2. Sanz MA, Lo-Coco F. Modern approaches to treating acute promyelocytic leukemia. *J Clin Oncol*. 2011;29(5):495-503.
3. de Thé H, Pandolfi PP, Chen Z. Acute promyelocytic leukemia: a paradigm for oncoprotein-targeted cure. *Cancer Cell*. 2017;32(5):552-560.
4. Chen SJ, Chen Z. Targeting agents alone to cure acute promyelocytic leukemia. *N Engl J Med*. 2013;369(2):186-187.
5. Estey E, Garcia-Manero G, Ferrajoli A, et al. Use of all-trans retinoic acid plus arsenic trioxide as an alternative to chemotherapy in untreated acute promyelocytic leukemia. *Blood*. 2006;107(9):3469-3473.
6. 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.
7. Powell BL, Moser B, Stock W, et al. Arsenic trioxide improves event-free and overall survival for adults with acute promyelocytic leukemia: North American Leukemia Intergroup Study C9710. *Blood*. 2010;116(19):3751-3757.
8. Sanz MA, Montesinos P, Rayón C, et al; PETHEMA and HOVON Groups. Risk-adapted treatment of acute promyelocytic leukemia based on all-trans retinoic acid and anthracycline with addition of cytarabine in consolidation therapy for high-risk patients: further improvements in treatment outcome. *Blood*. 2010;115(25):5137-5146.
9. Iland HJ, Bradstock K, Supple SG, et al; Australasian Leukaemia and Lymphoma Group. All-trans-retinoic acid, idarubicin, and IV arsenic trioxide as initial therapy in acute promyelocytic leukemia (APML4). *Blood*. 2012;120(8):1570-1580, quiz 1752.
10. Lo-Coco F, Avvisati G, Vignetti M, et al; Study Alliance Leukemia. Retinoic acid and arsenic trioxide for acute promyelocytic leukemia. *N Engl J Med*. 2013;369(2):111-121.
11. Rego EM, Kim HT, Ruiz-Argüelles GJ, et al. Improving acute promyelocytic leukemia (APL) outcome in developing countries through networking, results of the International Consortium on APL. *Blood*. 2013;121(11):1935-1943.
12. 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.
13. Iland HJ, Collins M, Bradstock K, et al; Australasian Leukaemia and Lymphoma Group. Use of arsenic trioxide in remission induction and consolidation therapy for acute promyelocytic leukaemia in the Australasian Leukaemia and Lymphoma Group (ALLG) APML4 study: a non-randomised phase 2 trial. *Lancet Haematol*. 2015;2(9):e357-e366.
14. Lo-Coco F, Di Donato L, Schlenk RF; GIMEMA; German–Austrian Acute Myeloid Leukemia Study Group and Study Alliance Leukemia. Targeted therapy alone for acute promyelocytic leukemia. *N Engl J Med*. 2016;374(12):1197-1198.
15. 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.
16. O'Donnell MR, Tallman MS, Abboud CN, et al; National Comprehensive Cancer Network. Acute myeloid leukemia, version 2.2013.

J Natl Compr Canc Netw. 2013;11(9):1047-1055.

17. Zeidan AM, Gore SD. New strategies in acute promyelocytic leukemia: moving to an entirely oral, chemotherapy-free upfront management approach. *Clin Cancer Res*. 2014;20(19):4985-4993.

18. Torka P, Al Ustwani O, Wetzler M, Wang ES, Griffiths EA. Swallowing a bitter pill-oral arsenic trioxide for acute promyelocytic leukemia. *Blood Rev*. 2016;30(3):201-211.

19. Lancet JE. Postremission therapy in acute promyelocytic leukemia: room for improvement? *J Clin Oncol*. 2014;32(33):3692-3696.

20. Falchi L, Verstovsek S, Ravandi-Kashani F, Kantarjian HM. The evolution of arsenic in the treatment of acute promyelocytic leukemia and other myeloid neoplasms: moving toward an effective oral, outpatient therapy. *Cancer*. 2016;122(8):1160-1168.

21. 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.

22. Zhu HH, Wu DP, Jin J, et al. Long-term survival of acute promyelocytic leukaemia patients treated with arsenic and retinoic acid. *Br J Haematol*. 2016;174(5):820-822.

23. 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.

24. Jun M; Chinese Society of Hematology, Chinese Medical Association & Chinese Society of Hematologist, Chinese Medical Doctor Association. Chinese guidelines for diagnosis and treatment of acute promyelocytic leukemia (2014) [in Chinese]. *Zhonghua Xue Ye Xue Za Zhi*. 2014;35(5):475-477.

25. Chinese Society of Hematology, Chinese Medical Doctor Association, Chinese Medical Association, Chinese Medical Doctor Association. Chinese guidelines for diagnosis and treatment of acute promyelocytic leukemia (2018) [in Chinese]. *Zhonghua Xue Ye Xue Za Zhi*. 2018;39(3):179-183.

26. Lo-Coco F, Cicconi L. Outpatient oral treatment for acute promyelocytic leukemia. *N Engl J Med*. 2015;372(9):884-885.

27. Lo-Coco F, Cicconi L. Towards home-based treatment for acute promyelocytic leukaemia, with caution. *Lancet Oncol*. 2018;19(7):846-847.

28. Zhu HH, Hu J, Gu XF. Arsenic as traditional Chinese medicine provides new hope for overcoming high treatment costs of acute promyelocytic leukemia. *J Glob Oncol*. 2016;2(6):442-443.

29. Jiang H, Liang GW, Huang XJ, et al. Reduced medical costs and hospital days when using oral arsenic plus ATRA as the first-line treatment of acute promyelocytic leukemia. *Leuk Res*. 2015;39(12):1319-1324.

30. Zhu HH, Huang XJ. Oral arsenic and retinoic acid for non-high-risk acute promyelocytic leukemia. *N Engl J Med*. 2014;371(23):2239-2241.

31. Zhou AX, Yao BS, Wang K, Wang TE. Experience in the treatment of acute nonlymphocytic leukemia. *Shanghai J Trad Chinese Med*. 1986;2:15-16.

32. Lu DP, Qiu JY, Jiang B, et al. Tetra-arsenic tetra-sulfide for the treatment of acute promyelocytic leukemia: a pilot report. *Blood*. 2002;99(9):3136-3143.

33. 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.

34. Huang SL, Guo AX, Xiang Y, et al. Clinical study of the compound Qingdai tablets for the treatment of acute promyelocytic leukemia. *Zhonghua Xue Ye Xue Za Zhi*. 1995;16(1):26-28.

35. Qian L, Zhao Y. The Cooperation Group of Phase II Clinical Trial of Compound Huangdai Tablet. Phase II clinical trial of compound Huangdai tablet in newly diagnosed acute promyelocytic leukemia. *Chin J Hematol*. 2006;27(12):801-804.

36. Wang L, Zhou GB, Liu P, et al. Dissection of mechanisms of Chinese medicinal formula Realgar-Indigo naturalis as an effective treatment for promyelocytic leukemia. *Proc Natl Acad Sci USA*. 2008;105(12):4826-4831.

37. Zhu HH, Liu YR, Jia JS, Qin YZ, Zhao XS, Lai YY. Oral arsenic and all-trans retinoic acid for high-risk acute promyelocytic leukemia. *Blood*. 2018;131(26):2987-2989.

38. Zhu HH, Guo ZP, Jia JS, Jiang Q, Jiang H, Huang XJ. The impact of oral arsenic and all-trans-retinoic acid on coagulopathy in acute promyelocytic leukemia. *Leuk Res*. 2018;65:14-19.

39. Wang F, Jia JS, Wang J, et al. The kinetics of white blood cell and the predictive factors of leukocytosis under oral or intravenous arsenic as the first-line treatment for acute promyelocytic leukemia. *Leuk Res*. 2017;61:84-88.

40. Zhu HH, Qin YZ, Huang XJ. Resistance to arsenic therapy in acute promyelocytic leukemia. *N Engl J Med*. 2014;370(19):1864-1866.

41. Wang XB, Xi RG, Yao W, Lin Y. Study on pharmacokinetics of the compound realgar natural indigo tablets in healthy volunteers. *Pharm J Chin PLA*. 2002;18(5):265-267.

42. 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.

43. Sun F, Chen NN, Cheng YB. Compound realgar and natural indigo tablets in treatment of acute promyelocytic leukemia: a summary of experience in 204 cases [in Chinese]. *J Chin Integr Med*. 2008;6(6):639-642.

44. Xiang Y, Wang XB, Sun SJ, et al. Compound Huangdai tablet as induction therapy for 193 patients with acute promyelocytic leukemia [in Chinese]. *Zhonghua Xue Ye Xue Za Zhi*. 2009;30(7):440-442.

45. Chen YB, Xiang Y, Chang XH, et al. The effects of compound Huangqi tablets on the ECG QTC interval and ST-T for patients with acute promyelocytic leukemia. *J Clin Hematol (China)*. 2012;25(9):606-607.

46. Zhu HH, Qin YZ. Oral arsenic and retinoic acid for children with low-risk acute promyelocytic leukemia [abstract]. In: *Proceedings from the 7th International Symposium on Acute Promyelocytic Leukemia; 24-27 September 2017*; Rome, Italy. Abstract CO022.

47. Yang MH, Wan WQ, Luo JS, et al. Multicenter randomized trial of arsenic trioxide and Realgar-Indigo naturalis formula in pediatric patients with acute promyelocytic leukemia: Interim results of the SCCLG-APL clinical study. *Am J Hematol*. 2018;93(12):1467-1473.

48. Frankel SR, Eardley A, Lauwers G, Weiss M, Warrell RP Jr. The "retinoic acid syndrome" in acute promyelocytic leukemia. *Ann Intern Med*. 1992;117(4):292-296.

49. Camacho LH, Soignet SL, Chanel S, et al. Leukocytosis and the retinoic acid syndrome in patients with acute promyelocytic leukemia treated with arsenic trioxide. *J Clin Oncol*. 2000;18(13):2620-2625.

50. De Botton S, Dombret H, Sanz M, et al; The European APL Group. Incidence, clinical features, and outcome of all trans-retinoic acid syndrome in 413 cases of newly diagnosed acute promyelocytic leukemia. *Blood*. 1998;92(8):2712-2718.

51. 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.

52. Sanz MA, Montesinos P. How we prevent and treat differentiation syndrome in patients with acute promyelocytic leukemia. *Blood*. 2014;123(18):2777-2782.

53. 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.