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

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Summary

Background Intravenous arsenic trioxide plus all-trans retinoic acid (ATRA) without chemotherapy is the standard of care for non-high-risk acute promyelocytic leukaemia (white blood cell count ≤10×10⁹ per L), resulting in cure in more than 95% of cases. However, a pilot study of treatment with oral arsenic realgar-Indigo naturalis formula (RIF) plus ATRA without chemotherapy, which has a more convenient route of administration than the standard intravenous regimen, showed high efficacy. In this study, we compare an oral RIF plus ATRA treatment regimen with the standard intravenous arsenic trioxide plus ATRA treatment regimen in patients with non-high-risk acute promyelocytic leukaemia.

Methods We did a multicentre, non-inferiority, open-label, randomised, controlled phase 3 trial at 14 centres in China. Patients aged 18–70 years with newly diagnosed (within 7 days) non-high-risk acute promyelocytic leukaemia, and a WHO performance status of 2 or less were eligible. Patients were randomly assigned (2:1) to receive treatment with RIF-ATRA or arsenic trioxide-ATRA as the induction and consolidation therapy. Randomisation was done centrally with permuted blocks and stratification according to trial centre and was implemented through an interactive web response system. RIF (60 mg/kg bodyweight daily in an oral divided dose) or arsenic trioxide (0·15 mg/kg daily in an intravenous dose) and ATRA (25 mg/m² daily in an oral divided dose) were used until complete remission was achieved. The home-based consolidation therapy was RIF (60 mg/kg daily in an oral divided dose) or intravenous arsenic trioxide (0·15 mg/kg daily in an intravenous dose) in a 4-week on 4-week off regimen for four cycles and ATRA (25 mg/m² daily in an oral divided dose) in a 2-week on 2-week off regimen for seven cycles. Patients and treating physicians were not masked to treatment allocation. The primary outcome was event-free survival at 2 years. A non-inferiority margin of –10% was used to assess non-inferiority. Primary analyses were done in a modified intention-to-treat population of all patients who received at least one dose of their assigned treatment and the per-protocol population. This study was registered with the Chinese Clinical Trial Registry (ChiCTR-TRC-13004054), and the trial is complete.

Findings Between Feb 13, 2014, and Aug 31, 2015, 109 patients were enrolled and assigned to RIF-ATRA (n=72) or arsenic trioxide-ATRA (n=37). Three patients in the RIF-ATRA and one in the arsenic trioxide-ATRA did not receive their assigned treatment. After a median follow-up of 32 months (IQR 27–36), 67 (97%) of 69 patients in the RIF-ATRA group and 34 (94%) of 36 in the arsenic trioxide-ATRA group had achieved 2-year event-free survival in the modified intention-to-treat population. The percentage difference in event-free survival was 2·7% (95% CI, –5·8 to 11·1). The lower limit of the 95% CI for the difference in event-free survival was greater than the –10% non-inferiority margin, confirming non-inferiority (p=0·0017). Non-inferiority was also confirmed in the per-protocol population. During induction therapy, grade 3–4 hepatic toxic effects (ie, increased liver aspartate aminotransferase or alanine transaminase concentrations) were reported in six (9%) of 69 patients in the RIF-ATRA group versus five (14%) of 36 patients in the arsenic trioxide-ATRA group; grade 3–4 infection was reported in 15 (23%) of 64 versus 15 (42%) of 36 patients. Two patients in the arsenic trioxide-ATRA group died during induction therapy (one from haemorrhage and one from thrombocytopenia).

Interpretation Oral RIF plus ATRA is not inferior to intravenous arsenic trioxide plus ATRA for the treatment of patients with non-high-risk acute promyelocytic leukaemia. This study suggests that a completely oral, chemotherapy-free model might be an alternative to the standard intravenous treatment for patients with non-high-risk acute promyelocytic leukaemia.

Funding Foundation for innovative research group of the National Natural Science Foundation of China, the Beijing Municipal Science and Technology Commission, the National Key R&D Program of China, and the National Natural Science Foundation of China.

Lancet Oncol 2018

Published Online
June 5, 2018
http://dx.doi.org/10.1016/S1470-2045(18)30295-X

See Online/Comment
http://dx.doi.org/10.1016/S1470-2045(18)30355-3

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Research in context

Evidence before the study

At the time of study design on Dec 1, 2013, we searched MEDLINE for articles published in any language between Jan 1, 1988, and Jan 1, 2013, using the search terms "acute promyelocytic leukaemia" AND "all-trans retinoic acid" OR "arsenic" OR "chemotherapy-free". We designed our study with the aim of identifying a completely oral (oral arsenic and ATRA) chemotherapy-free protocol for the treatment of patients with non-high-risk acute promyelocytic leukaemia.
Two chemotherapy-free protocols were already established: arsenic trioxide alone or ATRA plus arsenic trioxide.
Two single-arm studies showed 5-year overall survival in 64% and 74% of patients with arsenic trioxide treatment alone. Another single-arm study showed 3-year overall survival in 85% of patients using ATRA plus arsenic trioxide with or without gemtuzumab ozogamicin, which was confirmed by a randomised trial in which 99% of patients with non-high-risk acute promyelocytic leukaemia achieved 2-year overall survival. Because arsenic trioxide must be infused in the hospital, which is inconvenient, oral arsenic administration could have an advantage. However, none of the four studies focused on oral arsenic. No prospective randomised trials of oral arsenic plus all-trans retinoic acid (ATRA) without chemotherapy for the treatment of patients with non-high-risk acute promyelocytic leukaemia.

Added value of this study

To our knowledge, this study is the first randomised clinical trial comparing oral arsenic plus ATRA with intravenous arsenic trioxide plus ATRA in patients with non-high-risk acute promyelocytic leukaemia. We showed that a largely home-based treatment protocol with two oral targeted drugs without chemotherapy was effective and convenient. This study establishes a new treatment model for patients with non-high-risk acute promyelocytic leukaemia.

Implications of all available evidence

The results of this study show that non-high-risk acute promyelocytic leukaemia is curable using complete oral arsenic plus ATRA without conventional chemotherapy. Furthermore, this study suggests that a completely oral, chemotherapy-free model might be an alternative to the current frontline treatment for patients with non-high-risk acute promyelocytic leukaemia.

Introduction

Acute promyelocytic leukaemia is a subtype (M3) of acute myeloid leukaemia that arises from a distinct reciprocal translocation involving chromosomes 15 and 17, resulting in the promyelocytic leukaemia–retinoic acid receptor α (*PML–RARA*) fusion gene.[1] Acute promyelocytic leukaemia has become a curable disease using all-trans retinoic acid (ATRA)-containing chemotherapy or arsenic trioxide.[2–5] Non-high-risk patients (white blood cell count $\leq 10 \times 10^9$ cells per L) account for about 80% of all patients with acute promyelocytic leukaemia and more than 90% of these patients are cured by ATRA and chemotherapy. Several large multicentre trials[6–11] using ATRA and intravenous arsenic trioxide without chemotherapy have resulted in overall remission (complete response) in 94–100% of patients and long-term survival in more than 95% of patients. Thus, the combination of ATRA and intravenous arsenic trioxide without chemotherapy is considered the standard of care for newly diagnosed non-high-risk acute promyelocytic leukaemia according to the National Comprehensive Cancer Network guidelines.[12]

Arsenic trioxide must be infused in hospital, whereas oral arsenic can in some cases be administered outside of hospital. An oral realgar (As_4S_4)-containing formula named the realgar-Indigo naturalis formula (RIF), has exhibited anti-acute promyelocytic leukaemia activity.[13,14] Using a protocol that included chemotherapy in patients with acute promyelocytic leukaemia, we showed that the oral arsenic RIF provided an outcome similar to that produced with intravenous arsenic trioxide, with an advantage of cost-effectiveness.[15–17] Our pilot study showed high effectiveness and quality-of-life benefits of ATRA plus oral RIF without chemotherapy in patients with non-high-risk acute promyelocytic leukaemia.[18] All 20 patients were alive as of August 31, 2017, in complete molecular remission with a median follow-up of 48 months (IQR 44–50 months). However, these findings needed to be confirmed by a randomised study. Here, we present a randomised controlled trial with an aim to compare the efficacy and toxicity of oral RIF plus ATRA with standard intravenous arsenic trioxide plus ATRA in patients with newly diagnosed non-high-risk acute promyelocytic leukaemia.

See Online for appendix

Methods

Study design and participants

This study is a multicentre, open-label, non-inferiority, randomised, controlled, phase 3 trial done at 14 hospitals in China (appendix). The inclusion criteria were age 18–70 years, newly diagnosed (within 7 days) acute promyelocytic leukaemia classified as non-high-risk (white-cell count at diagnosis $\leq 10 \times 10^9$ per L),[19] a WHO performance status score of 0–2, a creatinine concentration of maximum three times the institutional upper limit of normal (ULN), alanine aminotransferase and aspartate aminotransferase concentrations of maximum 2·5 times the ULN, and a bilirubin concentration of maximum two times the ULN. Patients with comorbidities were permitted. Exclusion criteria were pregnancy, concomitant severe psychiatric condition, and clinically significant arrhythmias or electrocardiogram abnormalities. Initial enrolment and randomisation were solely based on morphological features, because treatment must be given immediately when acute promyelocytic leukaemia is

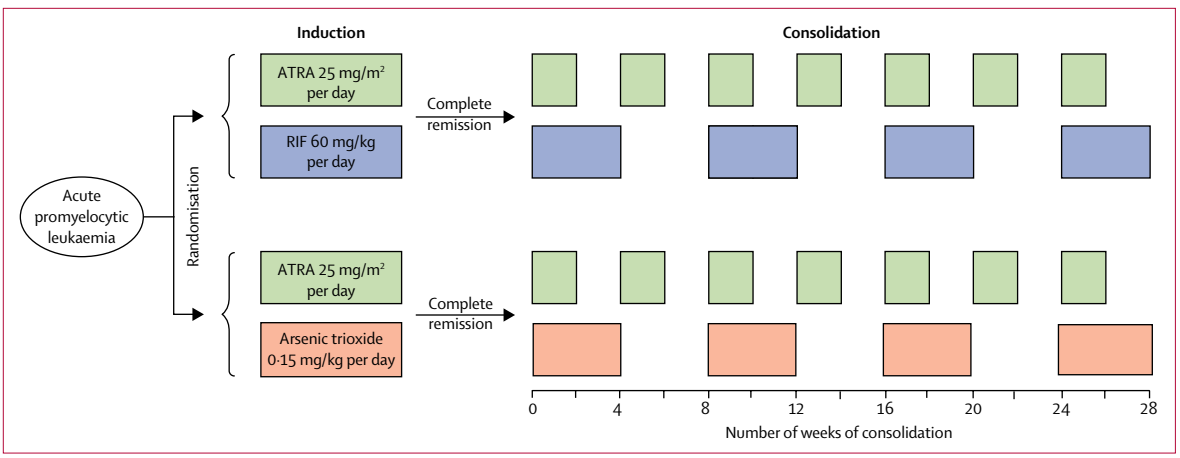

Figure 1: **Study design**
ATRA=all-trans retinoic acid. RIF=realgar-Indigo naturalis formula.

suspected. Genetic confirmation of the diagnosis was required for eligibility, but results take 5–7 days and so some patients were withdrawn from the study after randomisation on the basis of their genetic test results. A genetic diagnosis was established by detection of the *PML-RARA* fusion gene using an RT-PCR assay[20,21] or demonstration of the t(15;17) translocation via conventional karyotyping or fluorescence in-situ hybridisation. Written informed consent was obtained from all patients before study entry. This study was approved by the Ethics Committee of Peking University People's Hospital in Peking, China. The trial was done in accordance with the Declaration of Helsinki.

Randomisation and masking

In this open-label trial, eligible participants were centrally randomly assigned (2:1) to receive treatment with RIF-ATRA or arsenic trioxide-ATRA (the standard of care). Randomisation was done with permuted blocks (block size 6) and stratification by trial centre and was implemented through an interactive web response system. Up to 7 days of ATRA treatment before randomisation was allowed. The staff who administered the study drug received group assignment information based on the random number and then assigned the study drug to the nurses. Patients and study staff could not be masked to treatments because of the different routes of administration. The data analysis and assessment of outcomes were done in a masked manner.

Procedures

Patients received RIF-ATRA or standard arsenic trioxide-ATRA for induction and consolidation therapy. RIF (60 mg/kg bodyweight daily in three oral divided doses) or arsenic trioxide (one intravenous dose of 0·15 mg/kg daily) and ATRA (25 mg/m² daily in two oral divided doses) were used until complete remission was achieved, up to a maximum of 45 days (figure 1). We used ATRA 25 mg/m² daily because previous studies from the Hospital Saint Louis (Paris, France)[20] and the Shanghai Institute of Haematology (China)[21,22] showed that this lower ATRA dose had the same therapeutic effect as the conventional dose of 45 mg/m² daily (used as standard in Europe and the USA) but fewer side-effects, and 25 mg/m² is recommended by Chinese guidelines[23] for the diagnosis and treatment of acute promyelocytic leukaemia.[15,18] Anthracyclines were permitted when white blood cell count increased to 30×10^9 cells per L or more. All patients were admitted to hospital during induction therapy until recovery of coagulopathy and platelet count. Marrow assessment for complete response was done at the time of the absolute neutrophil count greater than $1\cdot0\times10^9$ cells per L and platelet count greater than 100×10^9 cells per L.

The consolidation therapy, which was taken by patients at home, included RIF (60 mg/kg daily in three oral divided doses) or intravenous arsenic trioxide (single dose of 0·15 mg/kg daily) in a 4-week on 4-week off regimen for four cycles and ATRA (25 mg/m² daily in two oral divided doses) in a 2-week on 2-week off regimen for seven cycles for approximately 7 months. The intravenous arsenic trioxide (10 mg per vial) was provided by Harbin Yida Pharmaceutical Company (Xiangfang, Harbin, Heilongjiang, China), and RIF (270 mg per tablet) was provided by the Yifan Pharmaceutical Co (Tianchang, China). RIF contained realgar (30 mg per tablet), *Indigo naturalis* (125 mg per tablet), *Radix salviae miltiorrhizae* (50 mg per tablet), *Radix pseudostellariae* (45 mg per tablet), and garment film (a cover to contain the drug components; 20 mg per tablet).

Guidelines for the prevention and management of coagulopathy, hyperleucocytosis, and haematological and non-haematological toxic effects were predefined in the protocol (appendix p 21). No prophylaxis for differentiation syndrome was recommended, but prompt use of dexamethasone (10–20 mg daily) was suggested on clinical suspicion of emergent differentiation syndrome until the disappearance of signs and symptoms for a minimum of 3 days.

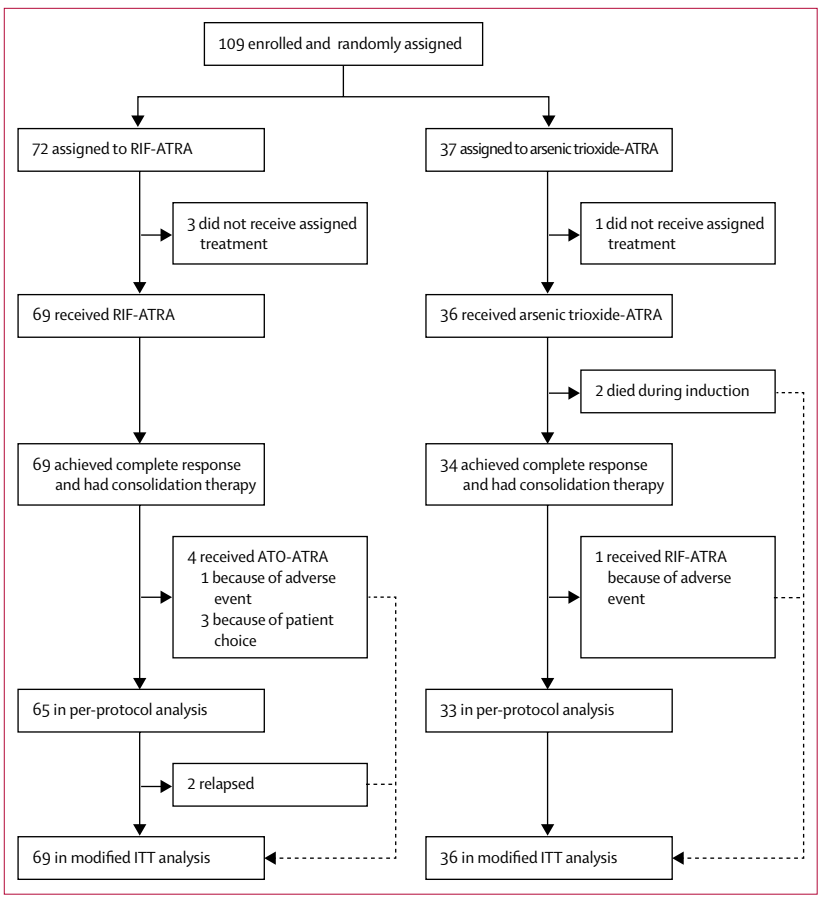

Figure 2: **Trial profile**
ATRA=all-trans retinoic acid. ITT=intention-to-treat. RIF=realgar-Indigo naturalis formula.

Follow-up assessments and bone marrow sample collections were done at before the start of treatment, upon achieving complete response, every 2 months during consolidation therapy, and then every 3 months thereafter for 2 years. Quantitative RT-PCR was performed as described in previous studies.[24,25]

Outcomes

The primary endpoint was the proportion of patients achieving event-free survival at 2 years. Events were defined as follows: no haematological complete response after induction therapy; no molecular complete remission after consolidation therapy, molecular relapse, haematological relapse; or death from any cause. Secondary endpoints were the proportion of patients achieving a haematological complete response, overall survival, cumulative incidence of relapse, and safety.

Overall survival and the cumulative incidence of relapse were defined according to the NCI workshop definitions. Haematological complete remission and haematological (morphological) relapse were defined according to the National Cancer Institute (NCI) workshop definitions.[26] Molecular complete remission was defined as the absence of detectable *PML-RARA* transcripts, and molecular relapse was defined as reversion to *PML-RARA* positivity, confirmed on serial samples after a previous negative result.[27] Toxic effects were graded according to the NCI Common Terminology Criteria for Adverse Events, version 3. Common haematological and non-haematological adverse events were monitored twice per week during induction and twice per month during consolidation. A post-hoc exploratory endpoint of disease-free survival was defined as the time from haematological complete remission to relapse (either molecular or haematological), the persistence of PCR positivity for *PML-RARA* after consolidation therapy, or death, whichever occurred first; data on patients who were still alive and in their first molecular complete remission were censored at the time of the most recent follow-up visit.

Statistical analysis

This trial was designed to test non-inferiority of event-free survival in the RIF-ATRA group compared with the arsenic trioxide-ATRA group at 2 years after start of induction therapy. Event-free survival was analysed as a binomial outcome rather than as a time-to-event outcome. A proportion of patients with event-free survival of 97% was assumed in the reference group.[9] We chose 10% as the non-inferiority margin since this margin preserves half of a minimum clinically acceptable proportion of the effect of the active treatment compared with a single arsenic trioxide controlled trial.[9,10,28–30] Based on a non-inferiority margin of –10%, a follow-up of 2 years, a type I error probability of 5%, and a power of 80% (considering the rarity of acute promyelocytic leukaemia and realistically successful completion of the trial), the sample size calculation done using the PASS software (version 11.0) established that 99 evaluable patients (2:1 per group) were required to draw a non-inferiority conclusion. When considering a withdrawal rate of 10%, 109 patients were required to be randomly assigned into two groups (73:36) in a 2:1 allocation.

Non-inferiority was concluded if the lower limit of the 95% CI for the difference in proportion of patients achieving event-free survival was greater than the –10% non-inferiority margin.

All efficacy analyses were based on a modified intention-to-treat population of participants who received at least one dose of assigned treatment. Patients who did not receive one dose of the assigned treatment were excluded from analyses. For the primary efficacy analysis, for non-inferiority, we also did a per-protocol analysis, which included patients who completed their assigned treatments as scheduled. All randomly assigned patients were followed up and assessed for all primary and secondary outcomes.

The survival curves were estimated using the Kaplan-Meier method and were compared using the log-rank test. Dichotomous variables were compared with Fisher's

exact test or the χ^2 test, and continuous variables were compared with the Wilcoxon rank-sum test. All statistical tests were two-tailed with a significance level of 0·05, except the non-inferiority hypothesis. The data were analysed using SAS software (version 9.4). This study is registered with the Chinese Clinical Trial Registry (ChiCTR-TRC-13004054), and the trial is complete.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

Between Feb 13, 2014, and Aug 31, 2015, 109 patients were enrolled and randomly assigned to RIF-ATRA (n=72) or arsenic trioxide-ATRA (n=37). Three patients in the RIF-ATRA and one in the arsenic trioxide-ATRA did not receive assigned treatment, but received ATRA and chemotherapy (figure 2). Median follow-up time was 32 months (IQR 27–36). The modified intention-to-treat analysis included all 105 patients who received at least one dose of the assigned therapy after randomisation. Baseline characteristics were not different between the two cohorts (table 1). The median age of the participants was 35 years (IQR 28–47), eight were older than 60 years.

In the modified intention-to-treat population, 67 (97%) of 69 patients in the RIF-ATRA group and 34 (94%) of 36 patients in the arsenic trioxide-ATRA group achieved 2-year event-free survival (table 2). The percentage difference in event-free survival between the two treatment groups was 2·7% (95% CI −5·8 to 11·1). The lower limit of the 95% CI for the percentage difference in event-free survival was greater than the −10% non-inferiority margin, confirming non-inferiority (p=0·0017). In the per-protocol analysis, 63 (97%) of 65 patients in the RIF-ATRA group and 31 (94%) of 33 patients in the arsenic trioxide-ATRA group achieved 2-year event-free survival. The percentage difference in event-free survival between the groups was 3·0% (95% CI −6·1 to 12·3), also confirming non-inferiority (p=0·0025).

69 patients in the RIF-ATRA group and 36 patients in the arsenic trioxide-ATRA group were evaluable for a response to induction therapy. All 69 patients in the RIF-ATRA group and 34 (94%) of 36 in the arsenic trioxide-ATRA group achieved haematological complete remission (p=0·12; table 2). The median time to haematological complete remission was 30 days (IQR 28–32) in the RIF-ATRA group and 30 days (28–35) in the arsenic trioxide-ATRA group (p=0·32). 53 (78%) of 68 patients in the RIF-ATRA group and 25 (74%) of 34 in the arsenic trioxide-ATRA group had achieved molecular remission (ie, were *PML-RARA* negative) 3 months after diagnosis (p=0·63). The median time to molecular remission was 3 months (IQR 2–4) for each group. All surviving patients in both groups (69 in the RIF-ATRA group and 34 in the arsenic trioxide-ATRA group) achieved molecular remission after consolidation therapy (appendix p 2).

	RIF-ATRA group (n=69)	Arsenic trioxide-ATRA group (n=36)
Age, years	34 (24–47)	36 (30–46)
Sex		
Men	33 (48%)	16 (44%)
Women	36 (52%)	20 (56%)
White blood cell count, 10^9 cells per L	2·01 (1·07–3·57)	2·12 (1·01–6·15)
Platelet count, 10^9 cells per L	30 (18–60)	25 (12–48)
Sanz risk		
Low	19 (28%)	13 (36%)
Intermediate	50 (72%)	23 (64%)
Blasts in bone marrow, %	82 (69–89)	84 (75–90)
PML-RARA/ABL, %	38 (29–52)	45 (16–70)

Data are n (%) or median (IQR). ATRA=all-trans retinoic acid. RIF=realgar-Indigo naturalis formula. Low Sanz risk=white blood cell count ≤10 × 10^9 cells per L and platelet count >40 × 10^9 cells per L. Intermediate Sanz risk=white-cell count ≤10 × 10^9 cells per L and platelet count ≤40 × 10^9 cells per L. ABL=ABL proto-oncogene 1, non-receptor tyrosine kinase.

Table 1: **Baseline characteristics of cohort**

	RIF-ATRA group (n=69)	Arsenic trioxide-ATRA group (n=36)	p value
Complete remission	69 (100%)	34 (94%)	0·12
Molecular remission after consolidation*	68 (100%)	34 (100%)	..
30-day mortality	0	2 (6%)	0·11
2-year event-free survival	67 (97%)	34 (94%)	0·49
2-year overall survival	69 (100%)	34 (94%)	0·049
2-year cumulative incidence of relapse	2 (3%)	0%	0·32

Data are n (%). ATRA=all-trans retinoic acid. RIF=realgar-Indigo naturalis formula. *Denominators for this measure are 68 in the RIF-ATRA group and 34 in the arsenic trioxide-ATRA group because the molecular result after consolidation was unavailable for some patients.

Table 2: **Clinical outcomes**

2-year overall survival was 100% in the RIF-ATRA group (n=69) and 94% (95% CI 87–100) in the arsenic trioxide-ATRA group (n=36; p=0·049; figure 3, table 2).

Estimated 2-year cumulative incidence of relapse was 3% (95% CI 0–7) in the RIF-ATRA group (n=69) and 0 in the arsenic trioxide-ATRA group (n=34; p=0·32; appendix p 3).

Two patients in the RIF-ATRA group relapsed during follow-up (one molecular relapse at 16 months and one haematological relapse at 18 months after complete response). ATRA and RIF were used as salvage therapy, and the two patients were alive and in second complete response until the final follow-up. No patients in the arsenic trioxide-ATRA group relapsed during follow-up (figure 3).

The number of red blood cell transfusions (three in the RIF-ATRA group *vs* four in the arsenic trioxide-ATRA group) and platelet transfusions (three *vs* three) received during induction were not different between the RIF-ATRA and arsenic trioxide-ATRA groups. Differentiation syndrome, including its moderate and severe forms,[31]

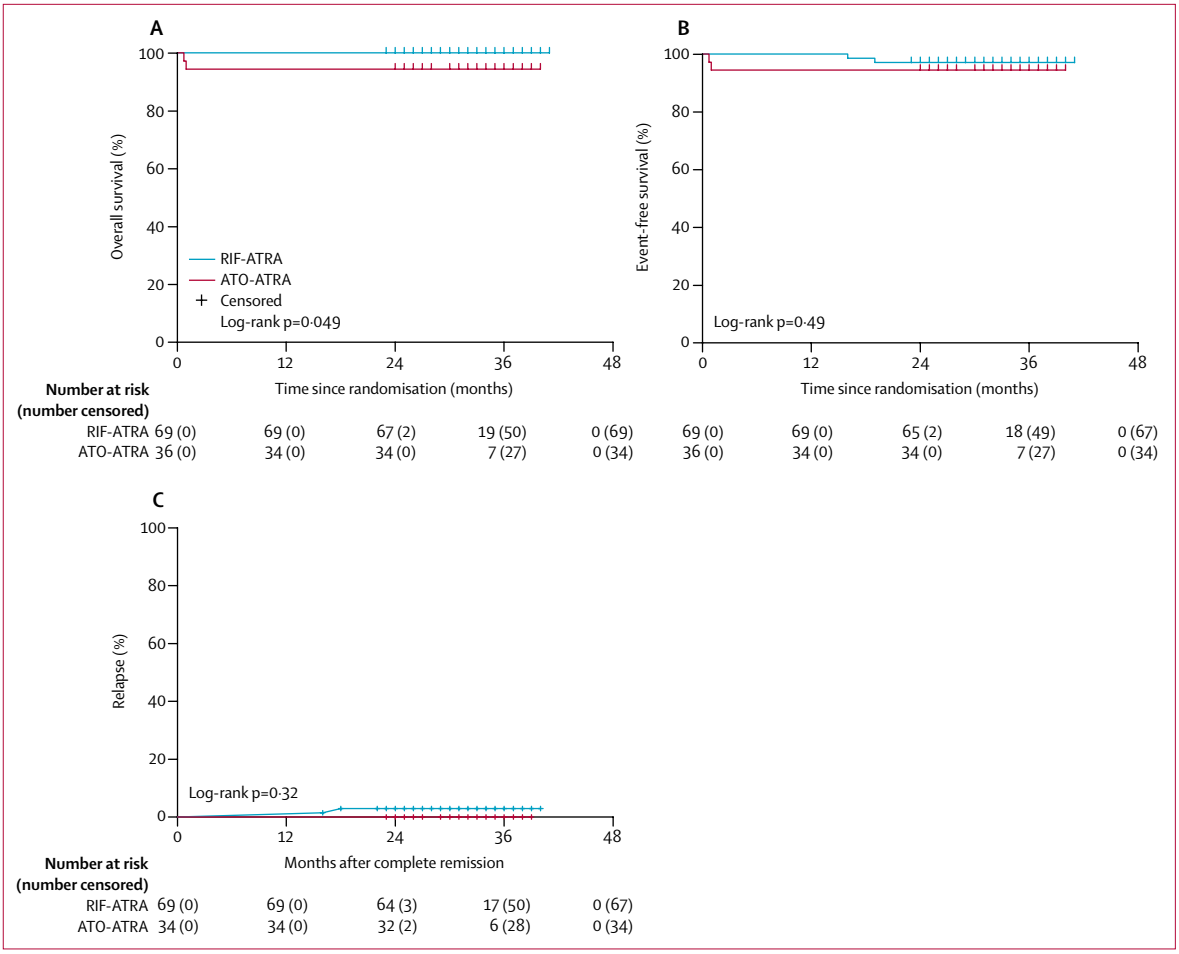

***Figure 3*: Kaplan-Meier plot of overall survival (A), event-free survival (B), and relapse (C)**
ATRA=all-trans retinoic acid. RIF=realgar-Indigo naturalis formula.

developed in 18 (26%) of 69 patients in the RIF-ATRA group and in ten (28%) of 36 patients in the arsenic trioxide-ATRA group. The median time of differentiation syndrome occurrence was 8 days in the RIF-ATRA group and 6 days in the arsenic trioxide-ATRA group. Severe differentiation syndrome occurred in two (3%) of 69 patients in the RIF-ATRA group and one (3%) of 36 patients in the arsenic trioxide-ATRA group and was fatal in one patient assigned to arsenic trioxide-ATRA.

Leucocytosis, defined as a white blood cell count greater than 10×10^9 cells per L, developed during induction therapy in 28 (41%) of 69 patients in the RIF-ATRA group and in 14 (39%) of 36 in the arsenic trioxide-ATRA group. All cases of leucocytosis were successfully managed with hydroxycarbamideor cytarabine therapy, or both, as recommended in the protocol. 46 (67%) of 69 patients in the RIF-ATRA group versus 26 (72%) of 36 patients in the arsenic trioxide-ATRA group received hydroxycarbamide, 15 (22%) versus 14 (39%) received cytarabine (p=0·49), and five (7%) versus eight (22%) received anthracyclines during induction.

During induction therapy, 40 (58%) of 69 patients in the RIF-ATRA group and 28 (78%) of 36 patients in the arsenic trioxide-ATRA group had grades 1–4 hepatic toxic effects (ie, increased liver aspartate aminotransferase or alanine transaminase concentrations; table 3). Grade 3–4 hepatic toxic effects were reported in six (9%) of 69 patients in the RIF-ATRA group versus five (14%) of 36 patients in the arsenic trioxide-ATRA group, and the toxic effects resolved with temporary discontinuation of arsenic, ATRA, or both. Grade 3–4 infection was reported in 15 (23%) of 64 patients in the RIF-ATRA group versus 15 (42%) of 36 patients in the arsenic trioxide-ATRA group (table 3). Six (9%) of 69 patients in RIF-ATRA group and five (14%) of 36 patients in arsenic trioxide-ATRA group required dose reductions during induction. Two patients in arsenic trioxide-ATRA died during induction therapy (one from haemorrhage and one from thrombocytopaenia).

103 of the 105 patients in haematological complete remission (69 in the RIF-ATRA group and 34 in the arsenic trioxide-ATRA group) proceeded to consolidation therapy.

	RIF-ATRA group (n=69)			Arsenic trioxide-ATRA group (n=36)		
	Grades 1–2	Grade 3	Grade 4	Grades 1–2	Grade 3	Grade 4
Nausea	14/66 (21%)	0	0	8/36 (22%)	1/36 (3%)	0
Vomiting	8/66 (12%)	0	0	3/36 (8%)	0	0
Diarrhoea	6/66 (9%)	0	0	2/36 (6%)	0	0
Mucositis	6/66 (9%)	0	0	5/36 (14%)	1/36 (3%)	0
Thrombosis or embolism	3/66 (5%)	0	0	0	0	0
Haemorrhage	22/66 (33%)	1/66 (2%)	1/66 (2%)	9/36 (25%)	2/36 (6%)	1/36 (3%)
Cardiac	4/66 (6%)	1/66 (2%)	0	2/36 (6%)	0	1/36 (3%)
Prolonged QTc interval	8/43 (19%)	0	0	6/31 (19%)	0	0
Infection	27/64 (42%)	14/64 (22%)	1/64 (2%)	12/36 (33%)	14/36 (39%)	1/36 (3%)
Increased liver ALT or AST concentrations	34/69 (49%)	6/69 (9%)	0	23/36 (64%)	4/36 (11%)	1/36 (3%)
Hyperbilirubinaemia	17/66 (26%)	0	0	13/36 (36%)	0	0
Raised creatinine	1/63 (2%)	0	0	0	1/34 (3%)	0
Neutropenia	6/66 (9%)	12/66 (18%)	42/66 (64%)	4/36 (11%)	7/36 (19%)	22/36 (61%)
Anaemia	22/66 (33%)	38/66 (58%)	5/66 (8%)	8/36 (22%)	19/36 (53%)	8/36 (22%)
Thrombocytopenia	5/66 (8%)	10/66 (15%)	45/66 (68%)	3/36 (8%)	9/36 (25%)	23/36 (64%)

Total numbers of patients vary because not all measures were recorded for all patients on the case report forms. ATRA=all-trans retinoic acid. RIF=realgar-Indigo naturalis formula. ALT=alanine transaminase. AST=aspartate aminotransferase. In the arsenic trioxide-ATRA group, one (3%) of 36 patients had grade 5 haemorrhage and one (3%) had grade 5 thrombocytopenia.

Table 3: **Incidence of all non-haematological and haematological toxic effects during induction treatment**

Four patients in the RIF-ATRA group and one in the arsenic trioxide-ATRA group crossed to the other group during consolidation therapy because of adverse events or patient choice. All 103 patients achieved complete remission after consolidation therapy. No patients died during the consolidation therapy. The post-hoc exploratory endpoint of estimated 2-year disease-free survival was 97% (95% CI 95–99) in the RIF-ATRA group (n=69) and 100% in the arsenic trioxide-ATRA group (n=36; p=0·32).

Discussion

This randomised controlled trial shows that RIF plus ATRA given for induction and consolidation therapy is not inferior to the standard intravenous arsenic trioxide plus ATRA for adults with non-high-risk acute promyelocytic leukaemia. The completely oral, chemotherapy-free outpatient treatment model of the RIF plus ATRA regimen has an antileukaemic efficacy similar to the standard treatment and could be more convenient to administer. In view of the convenience of administering oral arsenic (RIF), the rarity of acute promyelocytic leukaemia, and the high proportion of patients with non-high-risk acute promyelocytic leukaemia who achieve a cure (>95%) using standard ATRA plus intravenous arsenic trioxide treatments, we chose a non-inferiority study, which was more realistically achievable than a superiority study.

An important study by Lo-Coco and colleagues[9] showed that patients with non-high-risk acute promyelocytic leukaemia could be cured using only ATRA and intravenous arsenic trioxide without chemotherapy, which was confirmed by another large independent randomised trial in the UK.[10] We obtained similar results using a completely oral RIF and ATRA chemotherapy-free outpatient protocol for patients with non-high-risk acute promyelocytic leukaemia in a pilot study.[18] Our randomised controlled trial showed the efficacy and safety of the RIF-ATRA regimen.

Survival should be the primary endpoint for assessment of efficacy of a new treatment protocol for acute promyelocytic leukaemia. We chose 2-year event-free survival as the primary endpoint because the numbers of events reduces to almost zero after 2 years of treatment with ATRA and arsenic, according to the long-term follow-up results from previous studies.[17,32,33] Our results showed that 67 (97%) of 69 patients had achieved event-free survival at 2 years in the RIF-ATRA group compared with 34 (94%) of 36 in the arsenic trioxide-ATRA group; this arsenic trioxide-ATRA result is similar to results of two large independent randomised trials.[9,10] RIF might be a promising alternative to intravenous arsenic trioxide in the future. Moreover, the 100% estimated 3-year overall survival in the RIF-ATRA group supported the conclusion of our pilot study (a 4-year overall survival of 100%; Xhu H-H, unpublished). Several factors might have contributed to this high proportion of survivors. First, this study excluded patients with high-risk acute promyelocytic leukaemia. Second, series minimal residual disease monitoring rendered molecular relapses easily controlled by pre-emptive treatment. Third, the combination of arsenic and ATRA can eliminate leukaemic stem cells in acute promyelocytic leukaemia.[34]

The toxicity of arsenic-containing drugs is a major concern. This study showed no severe adverse effects with a cumulative dose of approximately 1500 mg of arsenic trioxide or 63 000 mg of realgar. We previously

showed that no significant arsenic accumulation occurred in plasma, urine, nails, or hair of patients after cessation of treatment for 1 year using a 1·8-times greater accumulative dose than the dose used in this study.[15] Therefore, we did not assess arsenic retention in this study. The most common adverse effect of the RIF-ATRA regimen was grade 1–4 hepatic damage (40 [58%] of 69 patients). However, grade 3 or 4 hepatic damage due to the arsenic trioxide-ATRA regimen in our study was markedly lower than that of the study reported by Lo-Coco and colleagues.[9] One possible explanation might be the use of a lower ATRA dose (25 mg/m² per day) in our study than in their study (45 mg/m² per day).[9]

One limitation of our study is that the median follow-up time was not long enough to draw definitive conclusions for overall survival, which is important for non-inferiority trials.[28] Second, we did not compare the economic differences between oral arsenic and intravenous arsenic in this chemotherapy-free protocol. In a protocol containing chemotherapy, we previously showed reduced medical costs when using oral arsenic plus ATRA as the first-line treatment of acute promyelocytic leukaemia compared with arsenic trioxide-ATRA.[16] We plan to perform economic analysis of the regimen from this study in future.

Our results suggest that non-high-risk acute promyelocytic leukaemia can be cured using complete oral arsenic plus ATRA without conventional chemotherapy. Although longer-term follow-up is needed to draw firm conclusions, our results support previously reported clinical and experimental evidence indicating that ATRA and arsenic act synergistically to eradicate acute promyelocytic leukaemia.[34]

Contributors

X-JH was the principal investigator. H-HZ and X-JH designed the study. H-HZ, D-PW, XD, XZ, LL, JM, Z-HS, H-YR, J-DH, K-LX, J-WW, Y-PS, M-YF, and JL recruited patients. X-YY and H-HZ validated and interpreted the data. X-YY and H-HZ did the statistical analysis. H-HZ wrote the paper and all authors reviewed and approved the final draft.

Declaration of interests

We declare no competing interests.

Acknowledgments

This study was supported by grants from the foundation for innovative research group of the National Natural Science Foundation of China (81621001), the Beijing Municipal Science & Technology Commission (Z141107002514004), the National Key R&D Program of China (2016YFE0202800), and the National Natural Science Foundation of China (81570128 and 81370639).

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