# Arsenic trioxide *versus* Realgar-Indigo naturalis formula in non-high-risk acute promyelocytic leukemia: a multicenter, randomized trial

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# SUPPLEMENTARY FILE

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Supplements of methods

**Institutions participating in APL16 study included:** The First Affiliated Hospital of Xi'an Jiaotong University, Tang-Du Fourth Military Medical University of Chinese PLA, Baoji People's Hospital, and Xi'an Gaoxin Hospital.

**Inclusion criteria**

- Age 14–75 years
- Newly diagnosed APL. (The genetic diagnosis was based on the presence of the t (15;17) or PML-RARA fusion genes.)
- Pre-treatment peripheral blood white blood cell (WBC) count < $10 \times 10^9$ /L
- Signed written informed consent provided by the patient or their family

**Exclusion criteria**

Exclusion criteria for this study included drug allergy, cardiac insufficiency (left ventricular ejection fraction less than 50%), inadequate renal reserve (creatinine greater than 3 times the upper limit of normal), significant arrhythmias or electrocardiogram abnormalities, other malignant tumors combined, pregnancy and lactation.

**Supportive care and monitoring**

Dexamethasone at a dosage of 10 mg every 12 hours was intravenously administered to patients suspected of having differentiation syndrome until signs and symptoms disappeared.

Patients with leukocytosis (defined as a peripheral WBC count greater than $10\times10^9$/L) were given 1g of hydroxyurea four times daily. No anthracycline or homoharringtonine was used to manage leukocytosis.

Patients with CNS leukemia require routine intrathecal therapy. No prophylaxis of CNS leukemia was regularly performed.

Dose adjustments or discontinuation of ATRA and ATO/RIF were implemented for patients who experienced grade 3 to 4 drug-related toxicity or differentiation syndrome.

Bone marrow aspirates were taken the day before the next treatment cycle to monitor PML-RARA expression during the consolidation therapy. We monitor bone marrow samples every 3 months after finishing the consolidation therapy. The observation lasted for 2 years.

**Definition of Outcomes**

Disease-free survival (DFS) is defined from enrolment to the time of any form of relapse or death.

Overall survival (OS) is defined from enrolment to the time of death due to any cause.

Adverse events were assessed using the Common Terminology Criteria for Adverse Events of the US National Cancer Institute, version 4. Adverse events during the induction therapy were divided into hematological and non-hematological.

Quality of life questionnaires were collected at 2 weeks after the end of induction therapy and at the end of the 3rd cycle of consolidation therapy.

Table S1. Incidence of hematologic and nonhematologic toxicity during induction therapy

| | Total | Grade1 | Grade2 | Grade3 | Grade4 |
|---|---|---|---|---|---|
| **Hematological toxicity** | | | | | |
| neutropenia | 100(92.6) | 8(7.4) | 12(11.1) | 34(31.5) | 46(42.6) |
| thrombocytopenia | 102(94.4) | 1(0.9) | 7(6.5) | 23(21.3) | 71(65.7) |
| anemia | 104(96.3) | 9(8.3) | 6(5.6) | 51(47.2) | 38(35.2) |
| leukocytosis | 66(61.1) | - | - | 61(56.5) | 5(4.6) |
| DIC | 34(31.5) | - | 20(18.5) | 11(10.2) | 3(2.8) |
| hemorrhage | 25(23.1) | 17(15.7) | 8(7.4) | 0 | 0 |
| **Non-hematological toxicity** | | | | | |
| increased AST or ALT | 66(61.1) | 47(43.5) | 14(13.0) | 5(4.6) | 0 |
| increased creatinine | 5(4.6) | 4(3.7) | 1(0.9) | 0 | 0 |
| heart failure | 9(8.3) | 3(2.8) | 4(3.7) | 2(1.8) | 0 |
| infection | 62(57.4) | 12(11.1) | 29(26.9) | 16(14.8) | 5(4.6) |
| prolonged QTc | 13(12.0) | 9(8.3) | 3(2.8) | 0 | 1(0.9) |
| nausea | 24(22.2) | 7(6.5) | 15(13.9) | 2(1.9) | 0 |
| vomit | 12(11.1) | 10(9.3) | 2(1.9) | 0 | 0 |
| diarrhea | 7(6.5) | 4(3.7) | 3(2.8) | 0 | 0 |
| mucositis | 14(13.0) | 8(7.4) | 5(4.6) | 1(0.9) | 0 |
| headache | 9(8.3) | 5(4.6) | 4(3.7) | 0 | 0 |

Data are expressed as n (%). Abbreviations: DIC, disseminated intravascular coagulation; AST, aspartate aminotransferase; ALT, alanine aminotransferase; QTc, the Corrected QT Interval.

Table S2. Plasma and urine arsenic concentrations measured in six patients in the ATRA-RIF group.

| ID | group | Date of test | Point of consolidation | Plasma arsenic concentrations (μg/L) | Urine arsenic concentrations (μg/L) |
|---|---|---|---|---|---|
| 1 | ATRA-RIF | 2017/7/16 | $6^{th}$ cycle | 75 | 1839 |
| 2 | ATRA-RIF | 2017/11/21 | $1^{st}$ cycle | 19 | 235 |
| 2 | ATRA-RIF | 2018/5/10 | $6^{th}$ cycle | 98 | 1737 |
| 3 | ATRA-RIF | 2018/1/4 | $1^{st}$ cycle | 79 | 896 |
| 3 | ATRA-RIF | 2018/7/1 | $6^{th}$ cycle | 61 | 650 |
| 4 | ATRA-RIF | 2018/1/17 | $1^{st}$ cycle | 76 | 1987 |
| 4 | ATRA-RIF | 2018/6/30 | $6^{th}$ cycle | 38 | 1368 |
| 5 | ATRA-RIF | 2018/5/10 | $2^{nd}$ cycle | 143 | 2181 |
| 5 | ATRA-RIF | 2018/9/22 | $6^{th}$ cycle | 19 | 174 |
| 6 | ATRA-RIF | 2018/9/20 | $5^{th}$ cycle | 58 | 591 |
| 6 | ATRA-RIF | 2018/10/19 | $6^{th}$ cycle | 39 | 1608 |

(Six patients, including three males and three females, in the ATRA-RIF group were randomized to blood and urine arsenic concentrations during the consolidation therapy. The blood and urine specimens were collected on the same day for each test.)

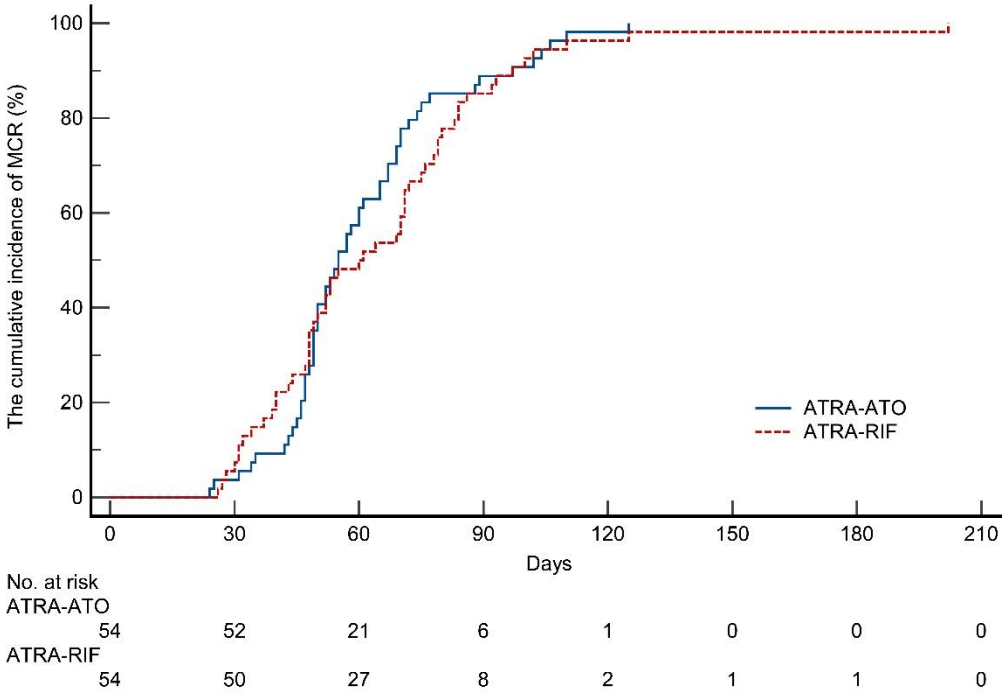


Figure S1. The cumulative incidence of molecular complete remission

Extended Table2. Incidence of Grade1-2 adverse events during consolidation therapy

| | ATRA-RIF(N=49) | ATRA-ATO(N=49) | *P* |
|---|---|---|---|
| | Grade 1-2 | Grade 1-2 | Grade 1-2 |
| Anemia | 10 (20.4, 9.1-31.7) | 15(30.6, 17.7-43.5) | .25 |
| Hemorrhage/thrombosis | 3 (6.1, 0-12.8) | 4(8.1, 8.2-15.8) | 1.0 |
| Increased AST or ALT | 7(14.3, 4.5-24.1) | 9(18.4, 7.5-29.2) | .59 |
| Hypertriglyceridemia | 25(51.0, 37.0-65.0) | 28(57.1, 37.6-76.6) | .69 |
| Nausea | 16(32.7, 16.7-49.5) | 18(36.7, 20.0-53.8) | .67 |
| Vomit | 10(20.4, 9.1-31.7) | 8(16.3, 6.0-26.7) | .60 |
| Diarrhea | 9(18.4, 7.5-29.2) | 3(6.1, 0-12.8) | .06 |
| Rash | 8(16.3, 6.0-26.7) | 7(14.3, 4.5-24.1) | .78 |
| Headache | 14(28.6, 15.9-41.2) | 11(22.4, 10.8-34.1) | .49 |
| Dry skin or mouth | 7(14.3, 4.5-24.1) | 9(18.4, 7.5-29.2) | .59 |
| Tinnitus | 3(6.1, 0-12.8) | 3(6.1, 0-12.8) | - |
| Prolonged QTc | 2(4.1, 0-9.6) | 4(8.2, 8.2-15.8) | .67 |
| Heart failure | 3(6.1, 0-12.8) | 4(8.2, 8.2-15.8) | 1.0 |
| Insomnia | 6(12.2, 3.1-21.4) | 8(16.3, 6.0-26.7) | .56 |

Data are expressed as n (%, 95% CI of the incidence).

Incidence of Grade 3-4 adverse events during consolidation therapy

| | ATRA-RIF(N=49) | ATRA-ATO(N=49) | *P* |
|---|---|---|---|
| | Grade 3-4 | Grade 3-4 | Grade 3-4 |
| Anemia | 0 | 1(2.0, 0-6.0) | - |
| Hemorrhage/thrombosis | 0 | 0 | - |
| Increased AST or ALT | 0 | 0 | - |
| Hypertriglyceridemia | 5(10.2, 1.7-18.7) | 2(4.1, 0-9.6) | .44 |
| Nausea | 1(2.0, 0-6.0) | 0 | - |
| Vomit | 0 | 0 | - |
| Diarrhea | 0 | 0 | - |
| Rash | 0 | 0 | - |
| Headache | 1(2.0, 0-6.0) | 0 | - |
| Dry skin or mouth | 0 | 0 | - |
| Tinnitus | 0 | 0 | - |
| Prolonged QTc | 0 | 0 | - |
| Heart failure | 0 | 0 | - |
| Insomnia | 0 | 0 | - |

Data are expressed as n (%, 95% CI of the incidence).