Proposal for the inclusion of arsenic therapies in the WHO Model list of ESSENTIAL MEDICINES for the treatment of acute promyelocytic leukemia.

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Introduction

Acute promyelocytic leukemia (APL) affects 7-10,000 people each year worldwide, including children and adults. It can be permanently cured more than 90% of the time with treatment regimens that combine ATRA, arsenic, and (in high-risk cases) chemotherapy. However, arsenic trioxide, an essential component of therapy, is not yet on the WHO list of essential medications, and in fact was not selected after review in 2015. A recent systematic review of the effectiveness of arsenic in APL patients concluded that arsenic added to ATRA-based regimens improved remission rates and event-free survival.[1] However, it is associated with QTc prolongation which can lead to cardiac dysrhythmias in patients who receive other drugs that prolong the QTc interval. Fortunately, cardiac toxicity is rare in APL patients who receive arsenic therapy and can largely be prevented by avoiding drug-drug interactions and careful monitoring. Most importantly, several recently published studies have definitively confirmed the superiority of ATRA/arsenic regimens over ATRA/chemotherapy, and arsenic-containing medications are now available from several suppliers in both intravenous and oral formulations, which has decreased cost and increased feasibility of arsenic-containing therapy for APL.[2-20] Finally, a review conducted for the UK National Institute for Health and Care Excellence (NICE) led the NICE Appraisal Committee to recommend approval of arsenic trioxide for newly diagnosed and relapsed APL.[11] Recently published clinical trials of ATRA plus arsenic and the role of oral arsenic formulations are discussed in the following sections.

1. **Name of the focal point in WHO submitting or supporting the application**
   Andre Ilbawi

2. **Name of the organization(s) consulted and/or supporting the application**
   International Pediatric Oncology Society (SIOP)

3. **International Nonproprietary Name (INN, generic name) of the medicine**
   - 3.1 Arsenic trioxide intravenous formulation
   - 3.2 Arsenic trioxide oral formulation
   - 3.3 Realgar-Indigo naturalis formula (RIF)

4. **Formulation proposed for inclusion; including adult and pediatric (if appropriate)**

4.1 Arsenic trioxide (trade name Trisenox and approved generics) is available in 10 mg/10 mL (1 mg/mL) ampules and is prescribed for use with all-trans-retinoic acid (ATRA) as part of comprehensive treatment regimens for newly-diagnosed or relapsed acute promyelocytic leukemia.

4.2 Realgar-Indigo naturalis formula (RIF) is the only commercially available oral arsenic product for acute promyelocytic leukemia. It is available as 270 mg tablets made by the Yifan Pharmaceutical Co (Tianchang, China). RIF contains Realgar (tetra-arsenic tetra-sulfide As_4S_4, 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).[2] The dose for frontline and relapsed acute promyelocytic leukemia is 60 mg/kg/day divided into 3 daily doses (20 mg/kg/dose).

4.3 International availability

4.3.1 Teva is the major produce of the originator branded arsenic trioxide (Trisenox), but recently several generics have entered the market and the patent for Trisenox expires in the USA this year.

4.3.2 Realgar-Indigo naturalis formula (RIF) originated as an herbal remedy in China (as did ATRA and arsenic trioxide), but has now been used successfully in several randomized clinical trials.[6,21,22] It is available from Anhui Tiankang Group Pharmaceutical Resin Company, Tianchang, Anhui, China as a formulation that contains Realgar (30 mg per pill), Indigo naturalis (125 mg per pill), Radix salviae miltiorrhizae (50 mg per pill), Radix pseudostellariae (45 mg per pill), and garment film (20 mg per pill). It is the only oral arsenic formulation commercially available and, as such, warrants special consideration, especially for use in low- and middle-income countries (LMIC) where the high cost of intravenous arsenic trioxide and the need for daily intravenous arsenic trioxide infusions over many months may pose important access and safety concerns. RIF has proven extremely effective in adults and children with frontline and relapsed APL in large randomized controlled trials, with event-free survival of 95-98% for newly-diagnosed patients, comparable to outcomes in the control arms which received intravenous arsenic trioxide.[3,23-33]

5. Approvals by major regulatory agencies

5.1 Arsenic trioxide

5.1.1 The U.S. Food and Drug Administration (FDA) approved arsenic trioxide in 2002 for relapsed APL and in 2017 for newly diagnosed patients, and in recent years use of regimens with ATRA plus arsenic has become the standard of care in high-income countries where arsenic therapies are readilya available. This is not surprising, since the combination of ATRA plus arsenic trioxide without chemotherapy has a 98% 5-year event-free survival in low-risk patients and above 90% in high-risk patients (usually combined with antrhacyclines).

5.1.2 The European Commission has granted marketing authorisation for arsenic trioxide for newly diagnosed in relapsed APL in 2002 (provisional approval) and 2010 (full approval), and many countries around the world have approved arsenic trioxide products available. Several generics are available in

India and the patent for originator (Trisenox) expires in most high-income countries in 2019.

5.1.3 The International Pediatric Oncology Society endorses the use of arsenic trioxide plus ATRA for newly diagnosed patients with APL and for relapsed patients and its members commonly use these medications (when reliably available) to manage low-risk, high-risk, and relapsed APL.

5.1.4 Generic versions are available from suppliers in several continents.

5.1 Realgar-Indigo naturalis formula (RIF) is a combination of Realgar (mineral tetra-arsenic tetra-oxide), Indigo naturalis (active ingredient indirubicin), and tanshinone that received regulatory approved for use in China in 2009 for frontline and relapsed acute promyelocytic leukemia. It is classified by the US National Cancer Institute as an herbal remedy with anti-cancer efficacy (https://www.cancer.gov/publications/dictionaries/cancer-drug/def/realgar-indigo-naturalis-formulation) but has not been submitted for approval by the FDA or EMA. Because of its low cost and the relative rarity of acute promyelocytic leukemia (7,000-10,000 cases per year globally) and the availability and affordability of intravenous arsenic trioxide in high-income countries, it is possible that RIF will not be submitted for regulatory approval in high-income countries, and will probably be used to serve the needs of patients in LMIC, where the cost and access to daily intravenous infusions (plus the cost of arsenic trioxide) may pose insurmountable barriers. Orsenix is developing an oral arsenic formulation that is produced as a pharmaceutical (as opposed to a naturally occurring product), which may become available in the future (**www.ClinicalTrials.gov** number NCT03048344), and an oral arsenic trioxide has been developed by Queen Mary Hospital in Hong Kong and used for several clinical trials, but is not commercially available.[23,24,32,34]

6. Whether listing is requested as an individual medicine or as an example of a therapeutic group?

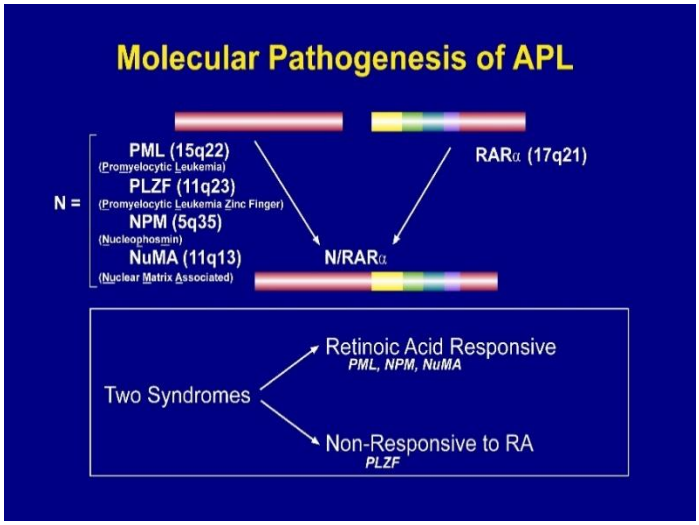
Arsenic trioxide previously has been submitted to the EML, so this new application focuses on clinical trial results that have been published in the past few years, and examines in detail the oral arsenic preparation RIF, which has not been previously submitted, but provides a feasible and inexpensive alternative to intravenous arsenic trioxide that could benefit many patients in low- and middle-income countries.

Arsenic trioxide and RIF are proposed as part of a therapeutic group that would include Trisenox, the originator intravenous arsenic trioxide, generic arsenic trioxides, and other arsenic compounds with proven efficacy to treat acute promyelocytic leukemia. Preparation of oral formulations will make treatment safer, less expensive, more feasible, and more accessible to patients, especially those in low- and middle-income countries, but has required modification from the arsenic trioxide originator, which has a low oral bioavailability.

7. Treatment details (requirements for diagnosis, treatment and monitoring)

7.1 Diagnosis of acute promyelocytic leukemia depends on clinical findings (hemorrhage and coagulopathy), laboratory findings (leukocytosis, anemia, thrombocytopenia), morphology (presence of myeloid blasts containing Auer rods), and documentation of the t(15;17) in the leukemia blasts by cytogenetics, FISH, or molecular biology (PCR).

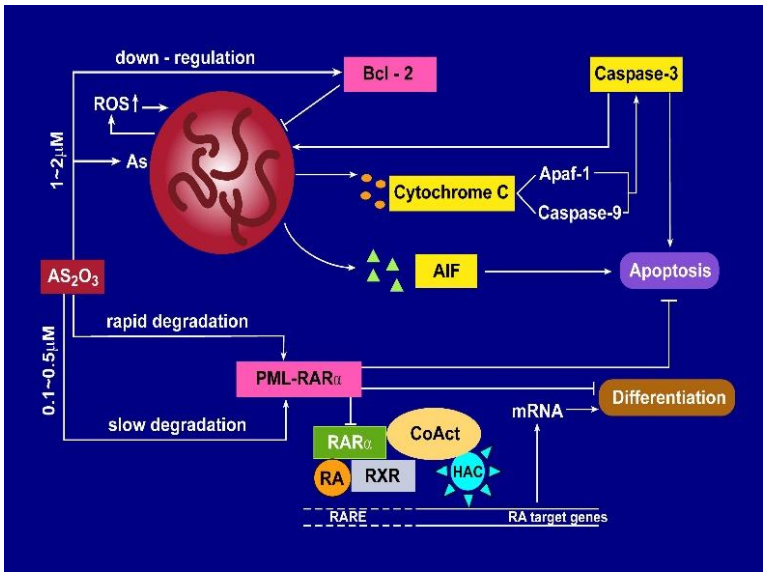
Figure 1. Diagnosis of APL requires detection of translocation t(15;17)



7.2 Risk stratification of patients allows each to receive the appropriate intensity of therapy to achieve cure, and includes a low-risk group, defined as patients whose presenting white blood cell count is less than 10,000 and a high-risk group (all other patients).

7.3 Treatment options for acute promyelocytic leukemia include remission induction, consolidation, and continuation therapy, which differ for low-risk and intermediate/high-risk patients. Low-risk patients can be cured 98% of the time with protocols comprised of ATRA plus arsenic and high-risk patients have cure rates above 90% using protocols that include ATRA, arsenic, and chemotherapy.

Figure 2. Differentiating agents ATRA and arsenic improve remission rates and reduce toxic death from coagulopathy by causing differentiation of promyeloblasts rather than tumor lysis.



Arsenic-ATRA-based regimens are more effective for newly diagnosed APL patients than chemotherapy-ATRA regimens

Many international cooperative group studies have now documented the superiority of ATRA plus arsenic therapy over ATRA plus chemotherapy, with less toxic death, higher remission rates, and improvements in disease-free and overall survival ranging from 11 to 20% in children, adults, and elderly patients.[35-45]

Arsenic-based regimens are effective for relapsed patients with APL

Arsenic-based regimens are effective for relapsed patients with APL, many of whom can be cured.[46-50] It was approved in the USA and Europe for this indication in 2002 and has been used routinely since that time. Indeed, protocols with arsenic alone have proven curative for some patients on both frontline and relapsed settings, but the highest cure rates have been documented with combinations of ATRA and arsenic therapy used in newly-diagnosed patients.

Figure 3. Use of ATRA and arsenic is standard of care for standard-risk APL and most regimens use blocks of therapy with different combinations of ATRA, arsenic, and chemotherapy

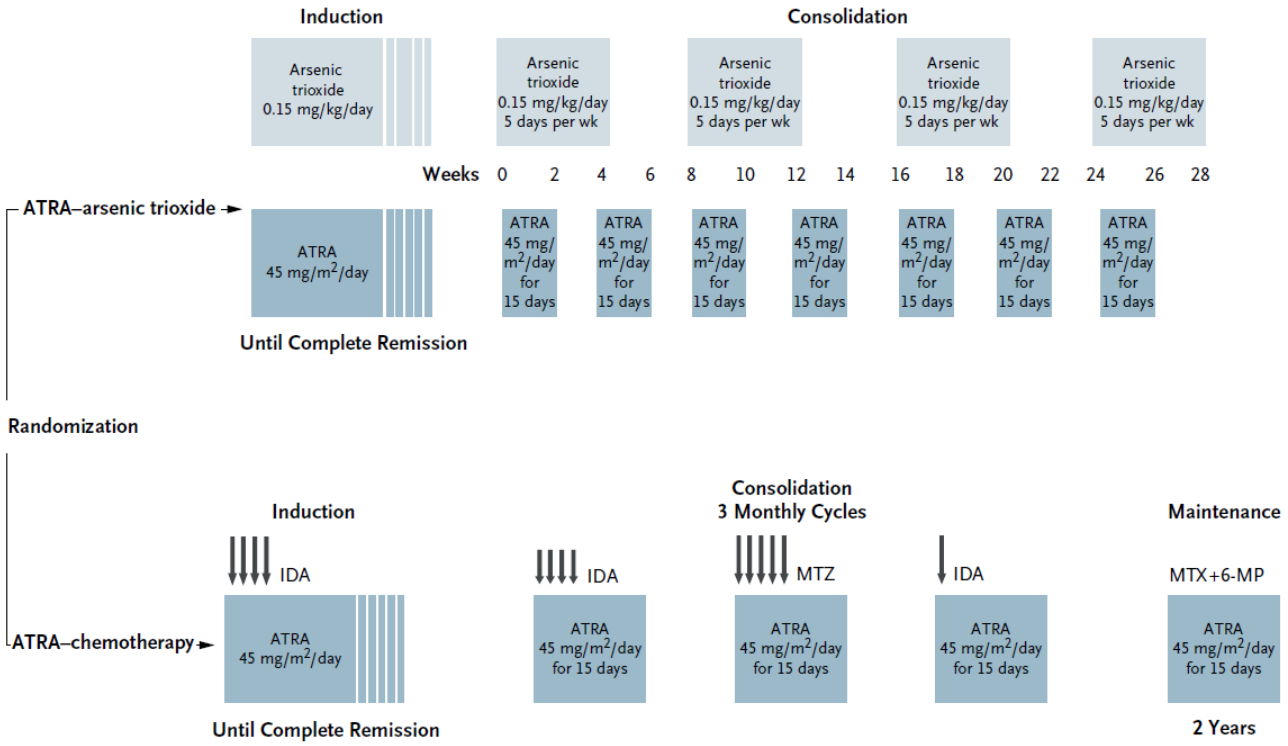


Figure 4. Treatment of APL with ATRA and arsenic improve event-free survival even in high-income countries, where toxic death rates are low

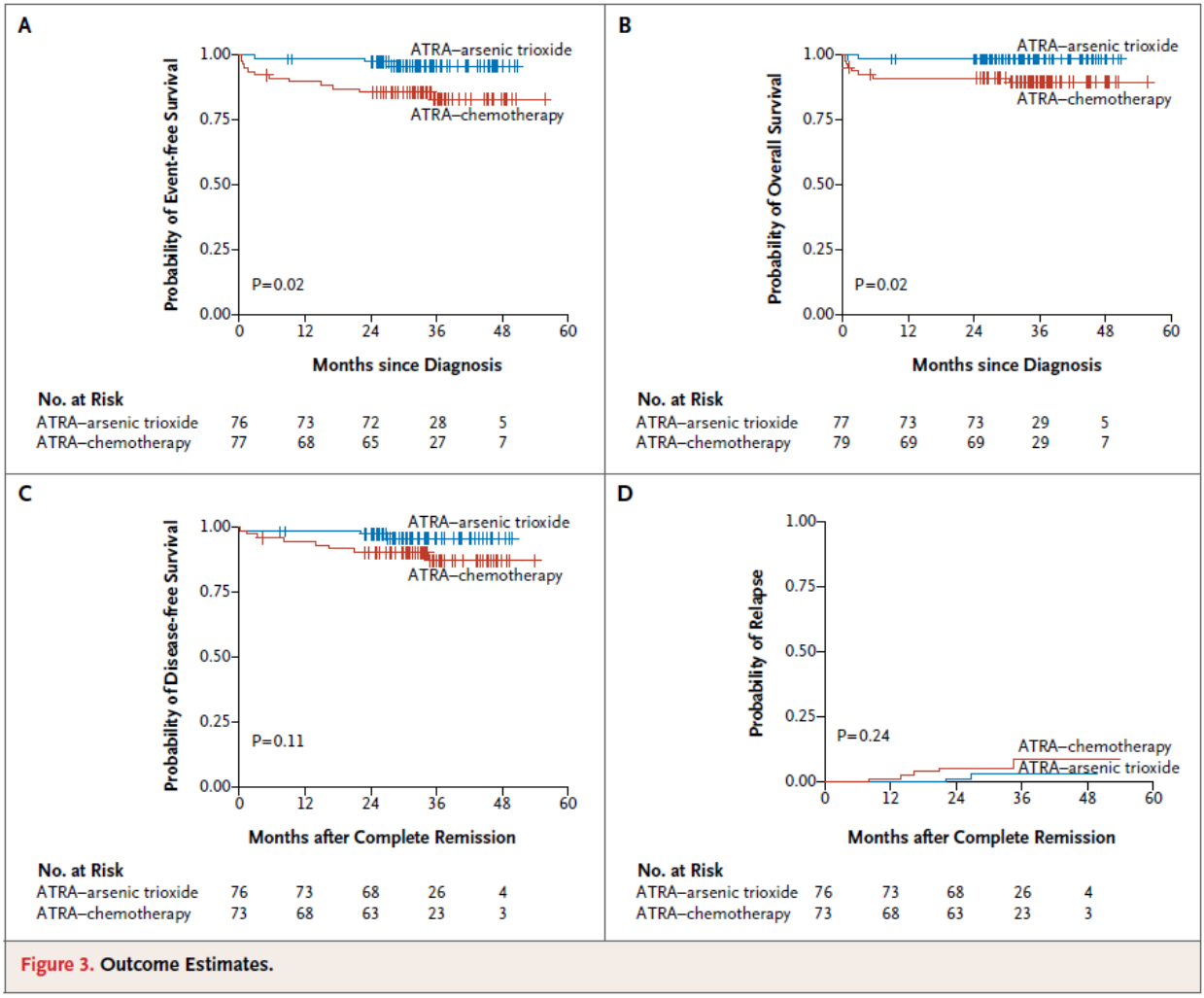


Figure 3. Outcome Estimates.

Table 1. Clinical trials using arsenic therapy for acute promyelocytic leukemia

Author	**Year**	**N**	**Induction**	**Consolidation**	**Maintenance**	**CR**	**D(E)FS (2 year unless otherwise specified)**	**OS (2 year unless otherwise specified)**
ATRA plus chemotherapy versus ATRA plus Arsenic								
Shen et al[51]	2004	61	**1** ATRA **2** ATO **3** ATRA +ATO	DNR/AraC/HA in all groups	**1** ATRA/6-MP/MTX **2** ATO/6-MP/MTX **3** ATRA/ATO/6-MP/MTX	>90% in all arms	**1** 13 months **2** 16 months **3** 20 months DFS	Not reported
Ravandi et al[52]	2009	82	ATRA/ATO (+GO in high risk group)	ATRA/ATO	none	92%	~80% EFS	~85%
Powell et al[53]	2010	481	ATRA/AraC/DNR	ATRA/DNR **vs.** ATRA/DNR/ATO	ATRA **vs.** ATRA/6-MP/MTX	90% in both arms	90% in ATO arm 70% in non-ATO arm DFS	86% in ATO arm at 3y 81% in non-ATO arm at 3y
Iland[54]	2012	124	ATRA/Ida/ATO	ATRA/ATO	6-MP/MTX/ATRA	95%	97.5% DFS	93%
Lo-Coco[55]	2013	156	ATRA/ATO **vs.** ATRA/Ida	ATO/ATRA **vs.** Ida/ATRA/MTZ	None (ATRA/ATO arm) **vs.** 6-MP/MTX/ATRA (ATRA/Ida arm)	ATRA, ATO: 100% ATRA, chemo: 95%	ATRA, ATO: 97% ATRA, chemo: 86% EFS	ATRA, ATO: 99% ATRA, chemo: 91%
Dai[56]	2009	90	ATRA, chemo vs. ATRA, ATO	ATRA, chemo vs. ATRA, ATO	ATRA, chemo vs. ATRA, ATO	92%	ATRA/chemo: 72% (RFS 3 years) ATRA/ATO: 93% (RFS 3 years) (p=0.002)	ATRA/chemo: Not specified ATRA/ATO: Not specified
Lou[57]	2013	137	ATRA/ATO	Chemo	ATRA/ATO/chemo		High-risk patients: 88% RFS, Intermediate/low-risk patients: 99%	98% 5-year survival
Zhu[25]	2013	235	ATRA/ATO vs. ATRA/RIF (oral arsenic)	Daunorubicin, cytarabine; homoharringtonine, mitoxantrone	ATRA/ATO vs. ATRA/RIF (oral arsenic)	97% in both groups	ATRA/ATO: 95.5% ATRA/RIF (oral arsenic): 98%	ATRA/ATO: 97% ATRA/RIF (oral arsenic): 99% (p=0.18)
Platzbecker[44]	2016	263	ATRA/ATO vs. ATRA/chemo			ATRA/ATO: 100%. ATRA/chemo: 97%	ATRA/ATO: 97%. ATRA/chemo: 80% (EFS, p<0.001)	ATRA/ATO: 99%. ATRA/chemo: 93%

Arsenic-based regimens for APL are less toxic than chemotherapy-based regimens
It is rare to identify new therapies that are more effective, less toxic, and less expensive than previous standards, but this is the case with arsenic therapies, and especially oral arsenic, for people with APL (Figures 4 and 5).[10,14,44,58-62] Finally, arsenic-based regimens have lower rates of second cancers than anthracycline-based regimens (though not statistically significant in the small studies conducted to date).[63]

Figure 5. Regimens comprised of ATRA and arsenic have lower toxicity than those including chemotherapy.

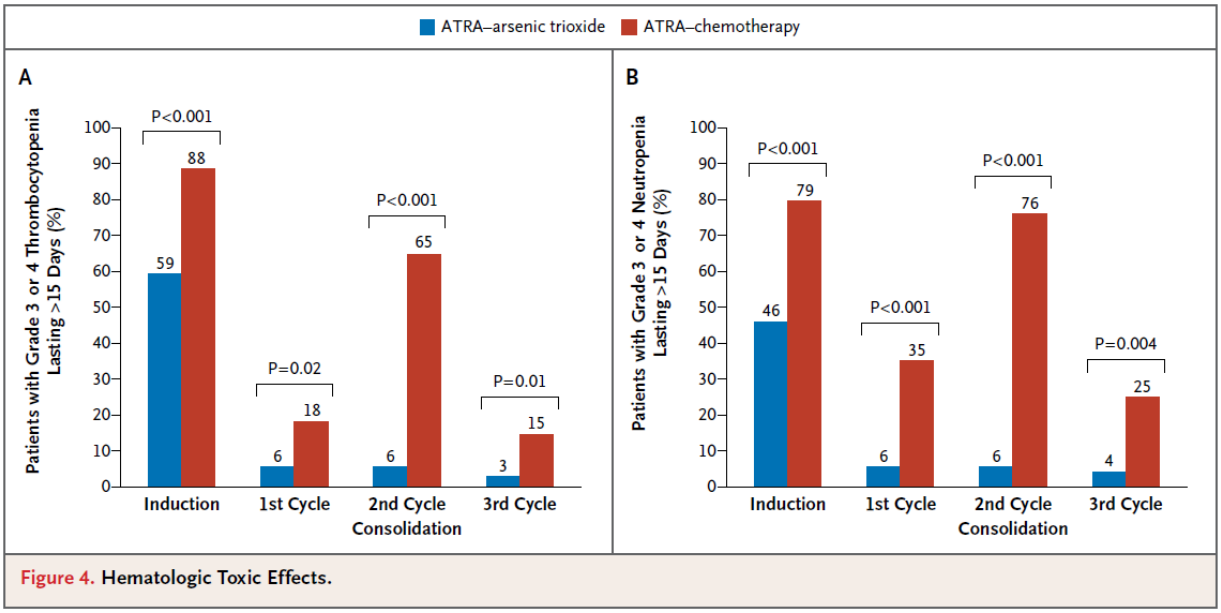


Figure 4. Hematologic Toxic Effects.

Importance of oral arsenic to make treatment safer, less expensive and more feasible, especially in low- and middle-income countries
Arsenic-based regimens cure more than 95% of patients with APL but require daily intravenous infusions during the arsenic-containing components of therapy. This means that patients must stay near the treatment center to receive daily infusions for 6 weeks during remission induction therapy followed by four 4-week blocks. Infusions are given over 1-2 hours and ideally administration should occur in an infusion center or hospital setting with availability of cardiac monitoring and resuscitation capabilities. Oral arsenic makes delivery of therapy more feasible in all countries, but is of particular relevance in LMIC, where logistical and financial barriers are numerous.

Realgar-Indigo naturalis formula
Realgar-Indigo naturalis formula (RIF), also known as Compound Huangdai has been used since 1988 and is made by combining mined ore, realgar, with Indigo naturalis, Salvia miltiorrhiza, and Radix psudostellariae as adjuvant components to assist the effects of realgar.[64] Multicenter clinical trials showed that a complete remission rate of 96.7% to 98% and a 5-year overall survival rate of 86.88% were achieved in APL patients receiving RIF, with moderate adverse effects such as gastrointestinal discomfort and rash.[64-66] Realgar, in combination with Indigo naturalis, also showed anti-APL activity.[67] The literature documents antitumor activity of S.

miltiorrhiza, whereas R. psudostellariae is thought to strengthen immune activity and seems not to be essential for RIF. Studies showed that tetraarsenic tetrasulfide (As_4S_4), indirubin, and tanshinone IIA are the major active ingredients of realgar, Indigo naturalis, and S. miltiorrhiza, respectively.[68-70] These results not only demonstrate the clinical efficacy of, but also suggest the possible synergistic effects of the combination, which was later confirmed in animal models dissecting the molecular and clinical effects of each component and combinations of components of RIF (Figure 6).[21]

Figure 6. After two decades of successful clinical use in humans with APL, the individual and combined activities of the ingredients of RIF were documented in cells lines and animal models.

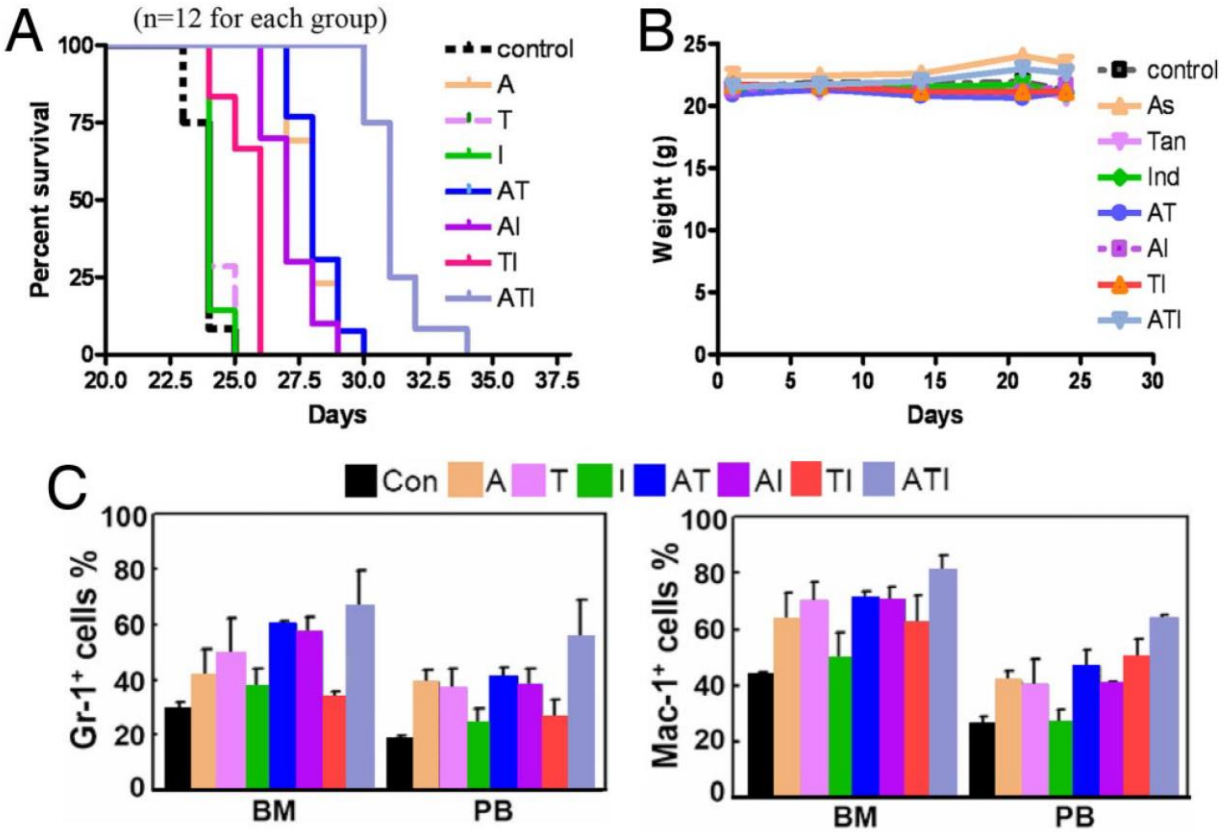


Figure description: In vivo therapeutic efficacies of tetra-arsenic tetra-sulfide, tanshinone, indirubin (ATI) on an APL murine model. (A) ATI significantly prolongs the life span of mice bearing PML-RAR alpha-positive leukemic cells compared with those treated with mono- or treatment with combinations of 2 of the three agents of A, T, and I ($P < 0.001$). (B) ATI does not cause loss of body weight, consistent with experience in human clinical trials in which toxicity of the regimen was limited. (C) Treatment with ATI resulted in cell maturation revealed by an accumulation of Gr-1 and Mac-1-positive cells in BM and peripheral blood (PB). (Dosage of agents used: Arsenic 10 mg/kg; tanshinone 50 mg/kg; indirubin 50 mg/kg. Arsenic was administrated intravenously and tanshinone and indirubin orally.

More importantly than the rationale for the activity of RIR are the many clinical trial results, including randomized clinical trial results of RIF versus arsenic trioxide in the context of ATRA-

based therapy. A large randomized trial of 242 patients aged 15 to 60 years with newly-diagnosed APL, randomly assigned subjects to regimens with arsenic (oral RIF versus intravenous arsenic trioxide) and ATRA followed by consolidation including chemotherapy (cytarabine, daunorubicin, mitoxantrone, homoharringtonine) and maintenance with ATRA plus arsenic were used. The induction death rate was less than 2% and 5-year survival and event-free survival were higher than 95% in both treatment arms (Figure 7).[25] Bioavailability and pharmacokinetics were almost identical using the two different arsenic preparations (Figure 8).[25]

Figure 7. Oral arsenic is safe, well-absorbed, and clinically effective for APL.

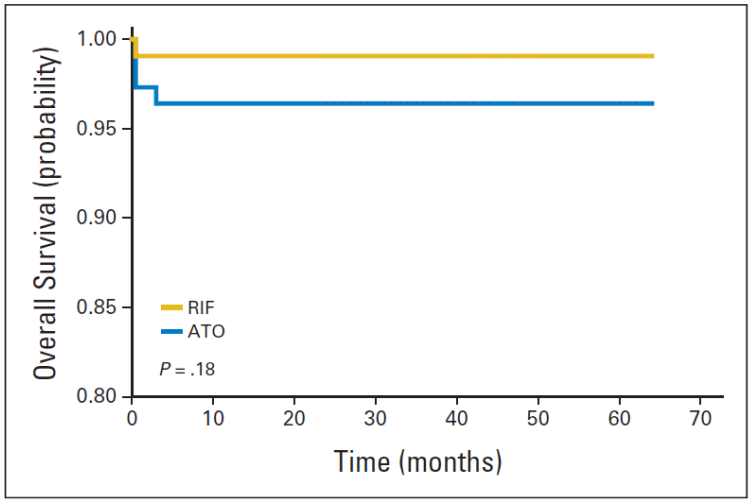


Fig 2. Overall survival of the Realgar-*Indigo naturalis* formula (RIF) and arsenic trioxide (ATO) groups.

Figure 8. Pharmacokinetics of oral (RIF) and intravenous (ATO) arsenic products are similar.[25]

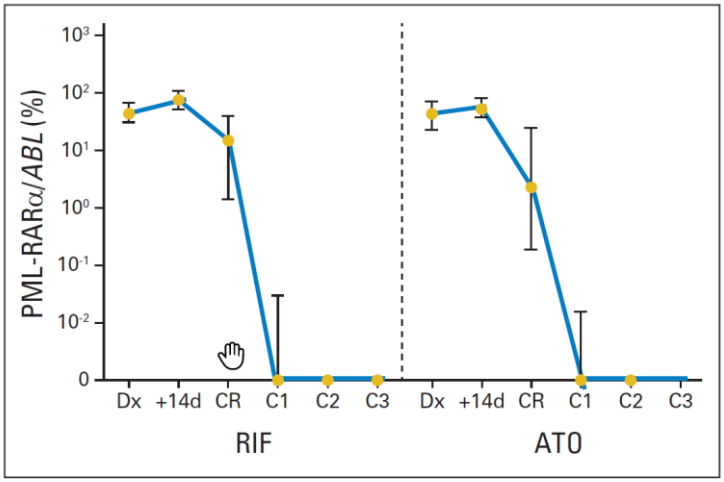


Fig 3. The molecular kinetics of the Realgar-*Indigo naturalis* formula (RIF) and arsenic trioxide (ATO) groups. +14d, 14 days after diagnosis; ATO, arsenic trioxide; CR, complete response; CR1, first CR; Dx, diagnosis; PML/RARα, promyelocytic leukemia/retinoic acid receptor alpha.

7.4 Monitoring of patients for complete response (by morphology) and molecular response (by FISH or PCR) at the end of induction establishes that the patient has attained a deep

(molecular) remission and can proceed to consolidation therapy. Once a patient is PCR-negative (no detectable minimal residual disease) monitoring is limited to clinical examination and interval complete blood counts. Repeated molecular testing is frequently performed in high-income countries for protocol-associated reasons but is not necessary for routine clinical care because the risk of relapse is extremely low and early detection of relapse has not been shown to improve outcomes. Furthermore, the cost of testing is significant and availability may be limited in LMIC, such that resources should be conserved for the two timepoints in which molecular testing is essential: at diagnosis and at the end of remission induction.

Oral arsenic is available in several forms, including arsenic trioxide (As_2O_3) similar to the intravenous formulation, which is not well-absorbed when the standard product is used. It is also available as an oral formulation, Realgar-Indigo naturalis formula (RIF) is the only commercially available oral arsenic product for acute promyelocytic leukemia. It is available as 270 mg tablets made by the Yifan Pharmaceutical Co (Tianchang, China). RIF contains Realgar (tetra-arsenic tetra-sulfide As_4S_4, 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).[2]

TABLE 1. Studies of Oral Arsenic for the Treatment of Patients With Acute Promyelocytic Leukemia[a]

Reference	Type of Study	Setting	No. of Patients	% High Risk	Induction	% HCR	% ED	Postremission Therapy		Best % Molecular CR[b]	Follow-Up, mo	Outcome
								Consolidation	Maintenance			
Kumana 2002[14]	Nonrandomized	Relapsed	5	Not available	ATO 10 mg IV d1 → ATO 10 mg/d PO d2 onward	100	0	ATO 10 mg PO		Not available	11	No deaths
Lu 2002[15]	Nonrandomized	Front-line, maintenance of CR1, relapsed	129	3 (21% of newly diagnosed patients)	RIF 50 mg/kg/d divided into 4 doses	100	0	RIF 2 wk on/2 wk off for 1 r	RIF 4 wk on/4 wk off for 3 y	80	Front line, 13.5; maintenance, 23; relapsed, not available	Front line: 3-y DFS, 76.6%; maintenance: 6-y DFS, 87.4%; relapsed, not available
Au 2003[55]	Nonrandomized	Relapsed	12	16	R1, ATO 10 mg/d; R2, ATO 10 mg/d + ATRA 45 mg/ms/d	R1, 100; R2, 80	8	R1, idarubicin; R2, same as induction for 6 2-mo cycles		92	R1, 14; R2, 17	R1, 87% of patients in continued CR2; R2, 80% of patients in continued CR3
Au 2011[56]	Nonrandomized	Maintenance of CR1	76	13	ATRA + chemotherapy (ATRA + ATO for patients aged >70 y)	NA	NA	Chemotherapy (patients aged ≤ 70 y)	ATO 10 mg/d (n = 20) or ATO 10 mg/d + ATRA 45 mg/ms/d (n = 19) or ATO 10 mg/d + ATRA 45 mg/ms/d + AA 1 g/d (n = 37)	NA	24	3-y DFS, 87.7%; 3-y EFS, 83.7%; 3-y OS, 90.6%
Firkin 2012[57]	Nonrandomized	Consolidation of CR1, relapsed	7	Not available	ATO 10 mg/d + ATRA 45 mg/ms/d	100[c]	0[c]	As2O3 (10 mg/d)	ATO 10 mg/d in relapsed patients	100[c]	Not available	71% alive; 57% in continued molecular CR
Zhu 2013[58]	Randomized, phase 3	Front line	117	19	ATRA 25 mg/ms/d + RIF 60 mg/kg/d	99	0.9	Sequential chemotherapy	ATRA 25 mg/ms/d for 2 wk/mo (in mo 1) → RIF 60 mg/kg/d for 2 wk/mo (in mo 2 and mo 3) for 2 y	100	39	2-y DFS, 98%; 3-y OS, 99%
Zhu & Huang 2014[59]	Nonrandomized	Front line	20	0	ATRA 25 mg/ms/d + RIF 60 mg/kg/d	100	0	ATRA 25 mg/ms/d + RIF 60 mg/kg/d 4 wk on/4 wk off for 7 mo		100	14	All patients in continued molecular CR

Abbreviations: AA, ascorbic acid; ATO, arsenic trioxide (As_2O_3); ATRA, all-*trans* retinoic acid; CR1, first complete remission; CR2, second complete remission; CR3, third complete remission; DFS, disease-free survival; ED, early death; EFS, event-free survival; HCR, hematologic complete remission; IV, intravenously; molecular CR, molecular complete remission; NA, not applicable; OS, overall survival; PO, orally; R1, first relapse; R2, second relapse; RIF, Realgar-*Indigo naturalis* formula containing tetra-arsenic tetra-sulfide or As_4O_4.

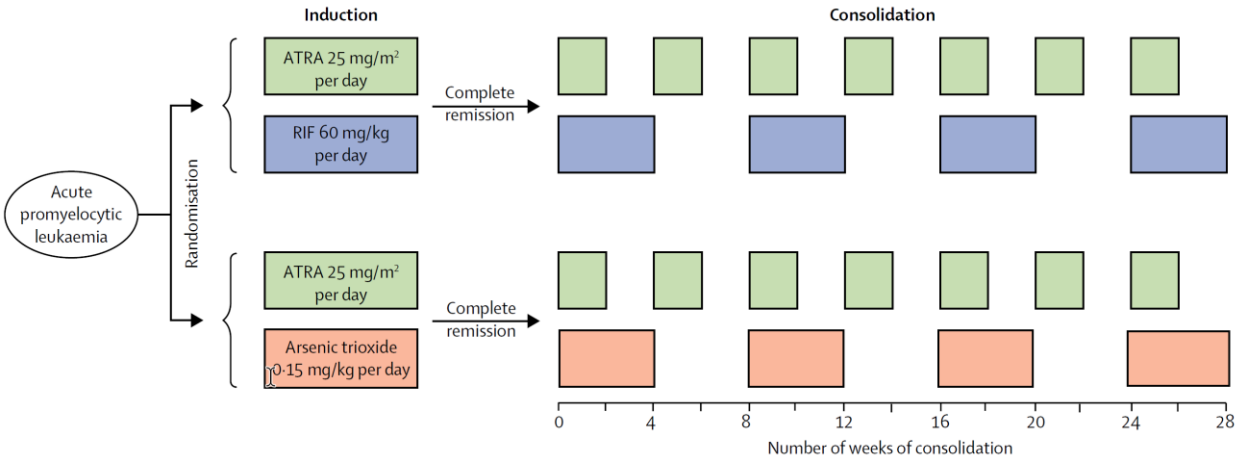
[a] Only clinical trials and series are reported in this table. Case reports and series with no efficacy and/or outcome data are not included.

[b] Percentages were derived from evaluable patients.

[c] N = 2 relapsed patients.

In addition to the studies listed above, recent randomized trials of ATRA plus oral RIF versus IV arsenic trioxide confirmed that RIF produces comparable outcomes in both children and adults and its long-term safety.[2,3,71]

Figure 9. Study design and excellent outcomes using ATRA plus RIF versus arsenic trioxide for non-high-risk acute promyelocytic leukemia.[2]



	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**

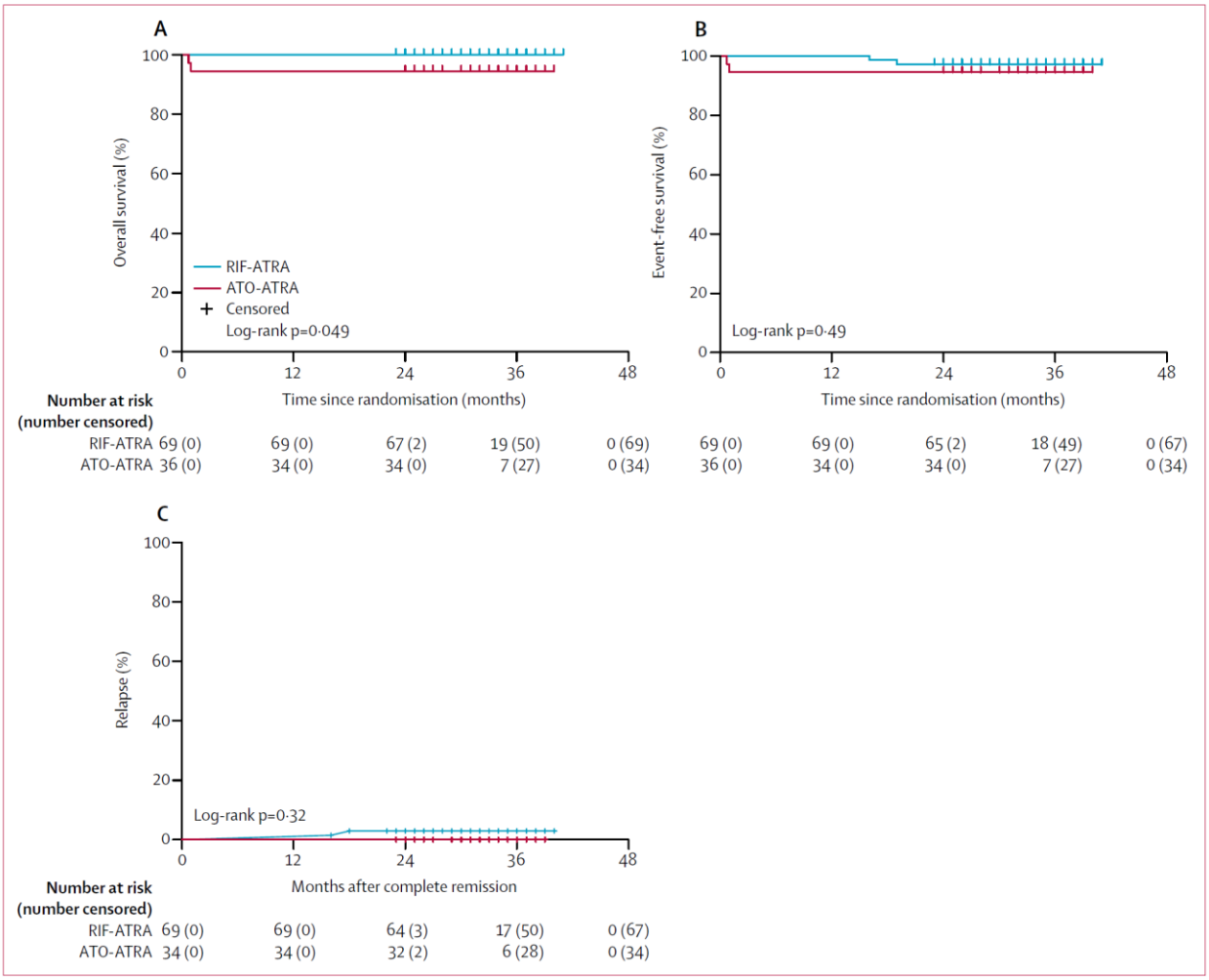


Figure 3: **Kaplan-Meier plot of overall survival (A), event-free survival (B), and relapse (C)**
ATRA=all-trans retinoic acid. RIF=realgar-Indigo naturalis formula.

Figure 10. Toxicity profile of RIF and arsenic trioxide

	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**

Both RIF and arsenic trioxide are well-tolerated, with few grade 3 or 4 toxicities other than myelosuppression (neutropenia, anemia, thrombocytopenia) related to the leukemia itself.

8. Information supporting the public health relevance.

Epidemiology of acute promyelocytic leukemia in children and adults
The true incidence of APL is not known. Until recently, population-based registries did not distinguish APL from other subtypes of AML, and the incidence of APL was estimated on the basis of its relative frequency among other AML subtypes in large clinical trials. In 2005, the expected incidence of AML in the USA was 11,930 cases (6,350 men and 5,580 women) per year 5. The Cancer Surveillance Program (CPS) of Los Angeles County has provided specific information about APL 6. In this registry, 107 (4.8%) of the 2,222 cases of AML registered between 1980 and 1995 were APL. This incidence is somewhat lower than the 5% to 13% reported by many large clinical trials and single institutions in the USA. Given the current limitations of population-based registries, the true number of newly diagnosed cases of APL per year in the USA is estimated to be 600 to 800 and globally 7,000 to 10,000 cases are expected each year, with disproportionate numbers of patients in LMIC relative to HIC.

Curability of acute promyelocytic leukemia
Although APL affects only 7-10,000 people each year, it is highly curable when ATRA and arsenic are available immediately at the time of diagnosis. Cure rates for low-risk patients who receive ATRA/arsenic-based regimens now approach 98% for low-risk patients and 90% for high-risk patients in HIC. However, curability in LMIC is greatly reduced, mostly due to early deaths prior to achieving remission. The early death approaches 30% in many LMIC, such that even if 90% of surviving patients are subsequently cured the cure rate overall is only 63%. Early deaths result predominantly from coagulopathy and hemorrhagic complications that are made worse by delayed diagnosis and delayed initiation of definitive therapy with ATRA plus arsenic. Addressing these barriers requires several simultaneous interventions: education of healthcare providers about the clinical features and curability of APL, availability of rapid diagnostic testing, dissemination of guidelines that encourage immediate use of ATRA if there is any clinical suspicion of APL (even before the diagnosis is confirmed), and immediate access to ATRA and arsenic therapies. When healthcare providers and patients have to find a supply of ATRA or arsenic at the time of diagnosis, the delays in access often prove fatal, so it is critical to have both medications on the EML and readily available in stock at pediatric and adult cancer centers.

9. Arsenic trioxide and related products for acute promyelocytic leukemia

Arsenic products are active for APL when used as monotherapy, but to achieve the relapse-free and overall survival rates of >95% that have been reported recently, it must be combined with ATRA and in some high-risk patients with chemotherapy in addition to arsenic/ATRA. There is no therapeutic substitute for arsenic products in APL, nor for

ATRA. Suitable concomitant chemotherapy for some high-risk patients (e.g. anthracyclines) is already listed on the EML.

10. Summary of comparative effectiveness in a variety of clinical settings:

Regimens containing arsenic plus ATRA yield survival rates 10-20% higher than regimens of ATRA plus chemotherapy and oral arsenic (RIF) yields results equivalent to those of intravenous arsenic trioxide, in the context of ATRA-containing regimens.

11. Summary of available data on comparative cost and cost-effectiveness within the pharmacological class or therapeutic group**

Arsenic trioxide was found to be highly cost-effective for relapsed APL in Canada using prices prevalent prior to the availability of generic formulations.[49] Cost-effectiveness in the frontline setting would be expected to be even higher, with very high remission rates and long-term survival, and decreased need for hospitalization, blood products, and supportive care. Use of an oral arsenic available at a low price point would improve cost-effectiveness even more by removing the need for daily infusions with cardiac monitoring.

12. Summary and Conclusions

i. Strength of recommendation: Very strong
ii. Rationale: Acute promyelocytic leukemia is curable in more than 95% of cases with the use of arsenic plus ATRA. Supportive care needs, costs, early toxicity, and permanent side effects are all lower with arsenic-containing regimens than with chemotherapy-based regimens.
iii. Efficacy and safety of arsenic/ATRA regimens compared to chemotherapy is even greater in low- and middle-income countries, where early deaths are common when regimens without ATRA and arsenic are used.
iv. The inclusion of arsenic products in the WHO EML will facilitate access to safe, affordable, high-quality treatment, and prompt treatment for acute promyelocytic leukemia, stimulate discussion around price-setting, and provide material to support inclusion in national EMLs and maintaining at least a minimum stock for urgent use at all centers where cancer patients are managed.

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