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The evolution of arsenic in the treatment of acute promyelocytic leukemia and other myeloid neoplasms

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Abstract

The therapeutic potential of arsenic derivatives has long been recognized and was recently rediscovered in modern literature. Early studies demonstrated impressive activity of this compound in patients with relapsed acute promyelocytic leukemia (APL). Over the last 2 decades intravenous arsenic trioxide has been used successfully, both alone and in combination with other agents for the treatment of APL and, with some success, other myeloid neoplasms. Arsenic trioxide is currently part the standard of care for patients with APL. More recently, oral formulations of this compound have been developed and are entering clinical practice. This review will discuss the evolution of arsenic in the treatment of APL and other myeloid neoplasms.

Keywords

arsenic trioxide; acute promyelocytic leukemia; oral arsenic

Introduction

Arsenic derivatives have been identified as compounds with therapeutic potential for over 2000 years in Greek and Chinese medicine. The first evidence of the efficacy of arsenic in leukemia was reported in 1882.(1) In the 1990s, researchers from China showed complete clinical remissions in two-thirds of patients with acute promyelocytic leukemia (APL) treated with arsenic, and a survival rate of 60% at 7 years.(2) At the same time, it was shown that arsenic trioxide (As_2O_3, ATO) induced apoptosis in APL cells via modulation of the PML-RARα protein.(3)

The combination of ATO and oral all-*trans* retinoic acid (tretinoin, ATRA) currently constitutes the standard of care for most patients with newly diagnosed and/or relapsed APL. The use of ATO has also been explored in many other hematologic malignancies. Since ATO can be part of induction, consolidation and maintenance therapy for most of these patients, but is given intravenously (IV) for long periods of time, there is a need for an alternative, more convenient oral route of administration of this drug. In this review, we discuss the

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impact of ATO in the treatment of APL and other myeloid neoplasms and the development of oral formulations of arsenic.

Pharmacology of ATO

Mechanism of action

The antineoplastic properties of ATO were first discovered in studies of APL, where this agent showed impressive activity. Almost all cases of APL are characterized by the hallmark cytogenetic lesion t(15;17), which generates the fusion gene PML-RARα.(4) Physiologically, heterodimers of RARα and its cofactor, retinoid X receptor (RXR), bind to retinoic acid response elements (RARE) within the promoter regions of target genes. In the absence of retinoic acid ligands, such binding results in the recruitment of co-repressor complexes and repression of transcriptional activity. PML is a component of PML nuclear bodies, protein-based nuclear structures that are involved in transcriptional regulation, apoptosis, cellular senescence, and DNA repair.(5) PML-RARα essentially acts as an aberrant RARα, in that it can oligomerize with RXR or other transcription factors and recruit co-repressors, ultimately resulting in the transcriptional suppression of genes that are critically important for granulocytic differentiation.(6) At therapeutic concentrations, ATRA binds the ligand-binding domain of PML-RARα and induces a conformational change in the oncoprotein structure, thus relieving the transcriptional suppression.(7)

In 2002 the FDA approved ATO for the treatment of relapsed/refractory APL. Multiple mechanisms of action have been invoked to explain the activity of ATO in APL, including induction of differentiation and apoptosis, inhibition of cell proliferation, and anti-angiogenic effects.(8) At higher concentrations (0.5 – 2.0 μmol/L) ATO predominantly induces apoptosis, whereas at lower concentrations (0.1 – 0.5 μmol/L) it promotes differentiation.(9) ATO–mediated apoptosis is mediated by its down-regulation of the human telomerase gene (hTERT).(10) Its anti-angiogenic effects may be due to the inhibition of the vascular endothelial growth factor.(8) ATRA and ATO synergistically interfere with the activity of PML-RARα, restoring gene transcription.(11) However, unlike ATRA, ATO has been shown to eradicate leukemia-initiating cells in murine APL models.

Pharmacokinetics

When administered IV, ATO is bound almost entirely to hemoglobin and quickly leaves the circulation to reach peripheral tissues. It tends to accumulate in hair, nails, liver, lungs, heart, and kidneys. Its terminal half-life is 12 ± 3 hours.(12) ATO is methylated in the body and excreted in the kidneys.(13) Continuous infusion of ATO does not appear to cause accumulation in plasma(12) and results in higher intracellular concentrations and rates of apoptosis, but reduced induction of differentiation, compared to daily 3–hour infusions.(14)

Oral ATO powder is not well absorbed in the gastrointestinal tract and causes significant gastrointestinal discomfort in most patients. Moreover, it is poorly soluble in water. To improve bioavailability, >99% pure As_2O_3 powder was mixed with sterile water and subsequently dissolved by adding 3 M sodium hydroxide. Finally, 6 M hydrochloric acid (HCl) and diluted HCl + sterile water were added to the solution and titrated to obtain a final

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pH of 7.2 and ATO concentration of 1mg/mL. In a pharmacokinetic study, 9 patients with relapsed APL were given 10 mg of ATO IV on Day 1 followed by a 10 mg oral ATO solution daily starting on Day 2. Although IV ATO reached higher peak plasma levels, the mean plasma and blood AUC values of the oral formulation were 99% and 87% of those of the IV formulation.(15)

Another oral arsenic-derivative is tetra-arsenic tetra-sulfide (As_4S_4). Realgar is a mined ore that mainly contains As_4S_4 (90%), as well as other types of arsenite, arsenic trioxide, and other minerals. High-purity As_4S_4 obtained from crystallized realgar was mixed with equal amounts of ground Seman platycladi as an excipient to shape capsules. Pharmacokinetics of this compound were analyzed in 7 volunteers with APL who achieved CR by using a single dose of As_4S_4. Arsenic was detected in the blood 30 minutes after oral administration and peaked at (3.4 ±1.4 hours). There was a wide interpatient variation in both the AUC and half-life of the drug. Over 90% of the molecule was eliminated in the urine within 72 hours, and all of it within 96 hours.(16) Because ATO is predominantly excreted through the kidneys, patients with renal dysfunction have increased exposure to ATO. Experiences in patients with severe kidney disease are anecdotal.(17) Importantly, ATO crosses the blood-brain barrier (achieving 15%–30% of plasma levels) when administered IV or orally.

Toxicity

In clinical studies conducted in patients with APL, the most common cause of death during induction was severe central nervous system (CNS) hemorrhage, in large part due to underlying disease-related coagulopathy. The second most frequent cause of death was APL differentiation syndrome, related to therapy, despite prophylactic cytoreductive therapy in patients who developed leukocytosis. As far as cardiac toxicity is concerned, while ATO is known to prolong the QT_C interval, cardiac arrhythmia was responsible for patients' death in a minority of cases. In addition, electrolyte imbalances and/or other drugs with QT-prolonging potential might have played a role in cardiac deaths in these studies.(18) Liver toxicity was described in about one third of the patients, but lead to treatment discontinuation in <10% of them (reviewed in (18)).

Intravenous ATO in APL

Relapsed disease

Early studies of ATO in relapsed APL conducted in Asia showed complete remission (CR) rates of around 60%, with estimated 5-year survival >90%.(2) ATO was subsequently tested more systematically in patients with relapsed APL. In general, these were non-randomized studies in which ATO was given IV (10 mg or 0.15 mg/kg daily until CR or up to 60 days). Anthracyclines or hydroxyurea were added for leukocytosis. Taken together, these studies included >300 patients. Objective responses were observed in 73%–100% of cases, and 85% of responders achieved CR. The median time to remission was variable (30–59 days), as was the rate of CR with undetectable PML/RARα transcripts (molecular CR).(19) Post-remission strategies varied across studies, with most patients receiving up to 5 additional courses of ATO-based therapy, and some proceeding to autologous or allogeneic stem cell transplantation (SCT). In non-transplant candidates, ATO seemed to yield better results

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when combined with either ATRA or chemotherapy for post-remission therapy compared to ATO alone.(20) SCT remains the preferred treatment for patients with relapsed APL who achieve a second remission. In a recent report of 37 patients with relapsed APL treated with ATO-based salvage regimens, 14 underwent autologous SCT, whereas 19 continued ATO-based therapy. After a median follow-up of 32 months, the estimated 5-year event-free survival (EFS) was 83% in patients who underwent SCT versus 34% in those who did not.(21) Limited data exist concerning the role of allogeneic SCT in this setting.

One important concept in the management of patients with APL is the difference between molecular and hematologic relapse. Among patients treated upfront with ATO-based regimens with or without SCT, 3-year relapse-free survival (RFS) and overall survival (OS) rates were 81% and 100% for the former, and 57% and 72% for the latter, respectively.(22) The most common site of extramedullary APL relapse is the CNS.(23) Treatment is based on the intrathecal administration of methotrexate and cytarabine +/− steroids or radiation therapy.(24) As noted above, because ATO can cross the blood-brain barrier, it may have anti-leukemic effects in the CNS. In a European registry study molecular CR rates were 62% in patients with molecular relapse, 74% in those with hematological relapse, and 100% in those with extramedullary relapse. Complications during induction were frequent in patients with hematological relapse, but absent in those treated at molecular relapse. The 3-year OS and cumulative incidence of relapse were 66%–68% and 41%–48%, respectively, in patients with hematological or molecular relapse and 90% and 11% in patients with extramedullary relapse, respectively.(25)

Front-line setting

ATO monotherapy—In light of the excellent results using ATO to treat patients with relapsed APL, this agent was tested in the front-line setting, to minimize the toxicity and enhance the clinical activity of standard induction regimens.

In a study of 197 patients, ATO was administered for a maximum of 60 days. The study was later amended to include up to four additional courses of ATO. The CR rate was 86% with a molecular CR rate of 92% in evaluable patients. The 5-year disease-free survival (DFS) was 67% and the 5-year OS was 64%.(26, 27) In a second series (72 patients), using a similar strategy, the CR rate and molecular CR rate were 86% and 76%, respectively.(28) An updated analysis of the same study reported DFS of 80% and OS of 74% at 5 years.(29) In both studies, the early death rate was 14% and was greater in patients presenting with leukocytosis. An important finding in these studies was that patients receiving consolidation therapy had better DFS than those who did not. Single-agent ATO was also tested in patients ≥60 years not candidates for ATRA–chemotherapy combinations. Eighty-eight percent of them achieve CR with no early deaths. At a median follow up of 99 months, the 10-year OS and DFS were 69% and 65%, respectively.(30)

ATO in combination with ATRA and chemotherapy—An important question is whether the addition of ATO to the combination of ATRA + chemotherapy might offer a survival advantage over ATRA + chemotherapy. Several studies have addressed this issue.

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In a phase III intergroup trial, 481 APL patients were randomized to receive ATRA + daunorubicin-cytarabine +/− ATO for 2 cycles prior to consolidation. The 3-year DFS, EFS, and OS were 90% vs. 70%, 80% vs. 63%, and 86% vs. 81%, respectively.(31) Using a similar strategy, in a multicenter North American study, 45 patients were treated with ATRA + daunorubicin followed by consolidation with cytarabine-daunorubicin for 3 days and ATO for an additional 30 days. Risk-adapted maintenance followed. Four patients died during induction. After a median follow-up of 2.7 years, the actuarial 3-year DFS and OS were 76% and 88%.(32) In a third study, 271 patients received consolidation therapy with either ATO- or high-dose cytarabine-containing regimens after induction with ATRA + daunorubicin. Estimated 5-year EFS and OS rates were 75% vs. 54% and 83% vs. 71% (P = 0.002), respectively. The benefit of ATO was observed in both low- and high-risk patients.(33) A few additional single-arm studies have incorporated ATO in the induction phase of therapy. In general, this strategy seemed feasible, with low early death rates, CR rates around 95%, and molecular CR observed in the majority of patients. DFS and OS rates were both over 95%.(34–36)

ATO in combination with ATRA without chemotherapy—Given the significant activity of both ATRA and ATO in patients with APL, the possibility of using these agents combined for induction therapy without cytotoxic chemotherapy was tested in clinical trials. In a single-arm study conducted at MD Anderson Cancer Center, ATO was combined with ATRA for induction therapy of patients with newly diagnosed APL. Gemtuzumab ozogamycin (GO) or idarubicin were for cytoreduction in patients with leukocytosis. Post-induction treatment consisted of 4 courses of ATO (daily for 5 days/week for 4 weeks every other month, for a total of 80 doses) + ATRA (2 weeks on/2 weeks off for 9 months) ± GO (if minimal residual disease-positive by PCR after ≥3 months of CR). The study included 82 patients. The CR rate was 92%, and 60 patients (73%) achieved a molecular CR. The early death rate was 9% and the estimated 3-year OS was 85%.(37, 38)

In a small randomized study (61 patients), patients received single-agent ATO, ATO + ATRA, or ATRA monotherapy for induction therapy.(39) The two single-agent arms were closed early due to inferiority, and the ATO + ATRA arm was expanded to include 85 patients. The authors reported a CR rate of 94% and molecular CR in all 31 evaluable patients. The early death rate was 6%, and the 5-year RFS and OS were 95% and 92%, respectively.(40)

In another study, 137 patients with newly diagnosed APL were treated with ATRA + ATO for induction, consolidation and (2-year) maintenance. The CR rate was 93% with a 7% early death rate. The 5-year OS and RFS were 99% for patients with low- and intermediate-risk disease, and 97% and 88%, respectively, for those with high-risk disease.(41) In a similar study, 90 patients with newly diagnosed APL received ATRA + ATO as induction and post-remission therapy. The CR rate of was 93%. ATRA + ATO post-remission therapy was associated with improved RFS at 3 years compared to ATRA + chemotherapy in responding patients (93% vs. 72%).(42) In a separate long-term study (84 patients, follow-up 70 months), the estimated 5-year EFS and OS were 89% and 92%, respectively, and the ATRA + ATO combination appeared to overcome the adverse prognostic significance of elevated WBC or FLT3 mutations.(40)

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By comparison, in four separate European studies patients with APL treated with ATRA + chemotherapy without ATO in any phase achieved OS of rates of 82–94%, EFS rates of 76% to not reached, and cumulative incidence of relapse of 8–12%. Patients aged ≥60 years had an early death rate of 19%, rising to 48% in non–study-eligible patients similarly treated, for a 7-year OS of 45%.(19)

Taken together, the above studies raise the question of whether ATRA + ATO can provide clinical benefit equal to that of ATRA + chemotherapy, but with less toxicity. On this basis, Lo-Coco et al. conducted a randomized non-inferiority trial of ATRA + ATO vs. ATRA + idarubicin in patients with newly diagnosed non-high-risk APL. Almost all patients achieved CR in both arms. At a median follow-up of 34.4 months, the 2-year EFS was 97% vs. 86% in the former vs. latter group ($P < 0.001$ for non-inferiority and $P = 0.02$ for superiority of ATRA + ATO). Similarly, OS rates were 99% vs. 91% ($P = 0.02$). Importantly, the ATRA + ATO combination was associated with less hematologic toxicity and fewer infections but greater hepatotoxicity.(43) This trial established ATRA + ATO as the standard of care for patients with newly diagnosed non-high-risk APL. A study with similar design in patients with *de novo* high-risk APL is currently underway.

ATO in other myeloid neoplasms

Because of its remarkable activity in APL, ATO has been tested in other myeloid and non-myeloid neoplasms, with mixed results. A discussion of the use of ATO in non-myeloid neoplasms is beyond the scope of this review.

Acute non-promyelocytic leukemia (ANPL)

ATO was initially tested in elderly patients with ANPL, either alone or in combination with other agents. Overall, the results have been disappointing. Early small studies had suggested that ATO alone is essentially ineffective in this setting. Roboz et al. conducted a phase 1/2 study of ATO combined with subcutaneous low-dose cytarabine in a group of difficult-to-treat elderly patients. The CR rate was 34% and death during induction was 8%.(44) In a recent phase 1 study, 11 ANPL patients who had either relapsed disease or were treatment-naïve but unfit for standard induction received ATO + ascorbic acid 5 days/week for 5 weeks. Among 10 evaluable patients, one achieved CR, one had marrow CR and 4 had <5% of blasts in bone marrow.(45) In another phase 1 study that included patients with myelodysplastic syndrome (MDS) and ANPL, escalating doses of ATO were combined with ascorbic acid and decitabine. Among 13 patients, only one achieved marrow CR. (46)

Despite these disappointing results in ANPL, recent evidence suggests that ATO and ATRA can promote the degradation of mutated NPM1 in AML cells, resulting in growth arrest and apoptosis, potentially offering a treatment approach for this subtype of leukemia.(47, 48)

Myelodysplastic syndrome

In initial studies in patients with MDS ATO yielded hematologic responses in about a quarter of patients, and one- to two-thirds of responders became transfusion-independent. (49)

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In a large phase 2 study (51 evaluable patients), patients received ATO (0.25 mg/kg/day) 5 days/week for 2 weeks every 28 days. Hematologic improvement rates were 39% and 9% in lower- and higher-risk patients, respectively. Transfusion reduction or independence occurred in 33% of patients. Median duration of response was 6.8 months.(50) In another phase 2 trial 115 patients received a loading dose of ATO followed by a maintenance regimen. The rate of hematologic improvement was 19% and the median response duration was 3.4 months.(51)

Several studies of ATO-based combinations in MDS were recently published.(52–55) Response rates were 17–30% and lasted up to 26 months depending on the patient risk group.

Chronic myeloid leukemia

In chronic myeloid leukemia (CML) cell lines, ATO was found to be potentially synergistic with imatinib. However, the first 3 patients with CML (in the accelerated phase) treated with imatinib and ATO obtained short-lived cytogenetic responses. In 16 patients with chronic phase CML and hematologic or cytogenetic progression, imatinib + ATO yielded one hematologic response and two major cytogenetic responses.(49)

Oral arsenic formulations

Currently, ATO is administered IV, thus necessitating daily clinic visits and administrations during induction (up to 60 days). This treatment requires hospitalization for at least the first two weeks. If a response is achieved, a second treatment cycle of 20–25 doses is given 5 days/week for 4–5 weeks (consolidation). Furthermore, vascular access must be maintained via a central venous catheter, with increased risk of infections. These limitations may prevent patients from receiving the most active APL therapy, especially when used as part of a long consolidation regimen. Due to these inconveniences and the high costs associated with prolonged daily infusions oral liquid formulations of this agent were developed.(15, 16) A synopsis of studies using various oral arsenic preparations for patients with APL is summarized in Table 1.

In the first study of oral ATO, 5 of the 9 patients treated obtained CR. No linear correlation was present between plasma and/or cellular ATO levels and response.(15) In a subsequent study, 12 patients with relapsed APL were treated with oral ATO at a dose of 10 mg daily until CR, followed by idarubicin consolidation. All patients achieved CR after a median of 37 days. At a median follow-up of 14 months, 7 patients maintained CR. Four of the 5 patients who relapsed were successfully salvaged with ATRA-oral ATO. Importantly, the PML/RARα transcript became negative in 11 patients. Reversible adverse events were elevation of liver enzyme levels, skin rash and headaches. No electrocardiographic abnormalities were reported.(56) In fact, the QT prolonging effects of oral ATO tended to be less compared to the IV formulation. Similar observations of efficacy and adverse effects were noted in an Australian experience.(57)

An oral solution of ATO was also tested as maintenance therapy for patients with APL who had achieved CR after induction and consolidation with daunorubicin-cytarabine and ATRA.

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Seventy-six patients received oral ATO for 2 weeks every 2 months for a total of 2 years. Once again, no significant EKG abnormalities were recorded. The 3-year DFS, EFS, and OS were 88%, 84%, and 91%, respectively.(58) Oral ATO has anecdotally been used in patients with end-stage renal disease on peritoneal dialysis (59) or hemodialysis,(60) or in those with liver transplant.(61)

The second arsenic-containing compound, As_4S_4 was tested in a pilot study of 129 patients with APL, 103 of whom were in first CR. Most patients with newly diagnosed or relapsed disease attained hematologic, cytogenetic and molecular CRs. Among patients who were in CR, 35 of 44 evaluable patients achieved molecular CR. The 3-year DFS in patients with relapsed disease and 6-year DFS in those in first CR were 76.6% and 87.4%, respectively. (16)

More recently, a randomized non-inferiority trial was conducted to compare an As_4S_4–containing formulation (Realgar-Indigo naturalis formula, RIF) (60 mg/kg) with IV ATO (0.16 mg/kg) in patients with previously untreated APL (n=242). Both formulations were combined with standard-dose ATRA for induction and maintenance. Consolidation consisted of 3 courses of conventional chemotherapy. Patients in both groups achieved similar CR rates (P = 0.62). After a median follow-up of 39 months, the 2-year DFS was 98.1% vs. 95.5% in the RIF vs. the ATO group. The difference in DFS was 2.6% (95% CI, −3.0% to 8.0%), which met the primary endpoint of <10% non-inferiority margin. OS was similar between the two groups (P = 0.18); the toxicity profiles were also similar.(62) Based on this study, the same group conducted another pilot study of RIF + ATRA without chemotherapy in 20 patients with non–high-risk APL. Post-remission therapy consisted of the same two agents given for up to 7 months. All 20 patients achieved CR in about 30 days and molecular CR (the primary endpoint) at 6 months. Differentiation syndrome occurred in 2 patients, and leukocytosis in 7. Importantly, 10 patients completed induction entirely without hospitalization. All patients received post-remission treatment at home, reporting a nearly normal quality of life.(63) A multicenter, randomized trial comparing ATRA combined with either RIF or IV ATO without conventional chemotherapy is underway in China. The issue of outpatient therapy for newly diagnosed APL, as it pertains to hemorrhagic complications, particularly in high-risk patients, remains controversial.(64)

Conclusions and future directions

ATO is an ancient drug that has recently been re-discovered as an important anti-leukemia agent, and has been successfully employed in the treatment of patients with newly diagnosed and relapsed APL, both as single agent and in combination with other agents. The combination ATO + ATRA is at least as effective as, and less toxic than ATRA + chemotherapy. This is now an established standard of care for patients with newly diagnosed low- and intermediate-risk APL. The optimal use of ATO in the consolidation and maintenance setting remains to be established. An oral liquid preparation of ATO was found to have equal activity and possibly more favorable toxicity profile than the IV formulation, and improved the patients' quality of life. Other derivatives of arsenic may be active in this setting too. An entirely oral, chemotherapy–free regimen might now become a reality for patients with newly diagnosed low- and intermediate-risk APL. In selected patients,

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treatment could be administered entirely in the outpatient setting. The results of ongoing trials seeking to replicate this success in patients with high-risk APL are awaited.

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Table 1

Studies of oral arsenic for the treatment of patients with APL

First author	Type of study	Setting	No.	% High-risk	Induction	% HCR	% ED	Post-remission therapy		Best % molecular CR*	Follow up, months	Outcome
								Consolidation	Maintenance			
Kumana(15)	Non-randomized	relapsed	5	na	ATO 10 mg IV day 1 -> ATO 10 mg/day PO day 2 onwards	100	0	ATO 10 mg PO		na	11	No death
Lu(16)	Non-randomized	frontline, maintenance of CR1, relapsed	129	3 (21% of newly diagnosed)	RIF 50 mg/kg/day divided in 4 doses	100	0	RIF 2 weeks on/2 weeks off for 1 year	RIF 4 weeks on / 4 weeks off for 3 years	80	Frontline: 13.5; Maintenance : 23; Relapsed: na	Front line: 3-yr DFS 76.6%; Maintenance: 6-yr DFS 87.4%; Relapsed: na
Au(56)	Non-randomized	relapsed	12	16	R1: ATO 10 mg/day R2: ATO 10 mg/day + ATRA 45 mg/ms/day	R1: 100 R2: 80	8	R1: Idarubicin; R2: same as induction for 6 2-month cycles		92	R1: 14; R2: 17	R1: 87% of pts in continued CR2; R2: 80% of pts in continued CR3
Au(58)	Non-randomized	maintenance of CR1	76	13	ATRA + chemotherap y (ATRA + ATO for pts > 70 yrs)	NA	NA	Chemotherapy (pts ≤70 yrs)	ATO 10 mg/day (20) or ATO 10 mg/day + ATRA 45 mg/ms/day (19) or ATO 10 mg/day + ATRA 45 mg/ms/day + AA 1 g/day (37)	NA	24	3-yr DFS 87.7%; 3-yr EFS 83.7%; 3-yr OS 90.6%
Firkin(57)	Non-randomized	consolidation of CR1, relapsed	7	na	ATO 10 mg/day + ATRA 45 mg/ms/day	100 §	0 §	As2O3 (10 mg/day)	ATO 10 mg/day in relapsed pts	100 §	na	71% alive; 57% in continued molecular CR
Zhu(62)	Randomized, phase 3	frontline	117	19	ATRA 25 mg/ms/day + RIF 60 mg/kg/day	99	0.9	Sequential chemotherapy	ATRA 25 mg/ms/day for 2 weeks/month, month 1 -> RIF 60 mg/kg/day for 2weeks/ month, months 2–3, for 2 years	100	39	2-yr DFS 98%; 3-yr OS 99%
Zhu(63)	Non-randomized	frontline	20	0	ATRA 25 mg/ms/day + RIF 60 mg/kg/day	100	0	ATRA 25 mg/ms/day + RIF 60 mg/kg/day 4 weeks on/4 weeks off, for 7 months		100	14	All pts in continued molecular CR

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

*in evaluable patients;

§in relapsed patients (2).

Note: only clinical trials and series are reported in this table. Case reports and series with no efficacy and/or outcome data are not included

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