pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Arsenic Trioxide (Trisenox) for Acute Promyelocytic Leukemia

February 18, 2014

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1 GUIDANCE IN BRIEF

1.1 Background

The purpose of this review is to evaluate the safety and efficacy of arsenic trioxide (ATO; Trisenox) as monotherapy or in combination with ATRA and/or other chemotherapy agents, on patient outcomes compared with appropriate comparators in treatment of patients with:

- Previously untreated (first-line) Acute Promyelocytic Leukemia (APL).
- Relapsed/Refractory Acute Promyelocytic Leukemia

Currently ATO has a Health Canada approved indication for use in induction of remission and consolidation in patients with APL who are refractory to, or have relapsed from, retinoid and anthracycline chemotherapy and whose APL is characterized by presence of the t(15;17) translocation of PML/RAR-alpha gene expression [22].

As per the Health Canada product monograph, induction treatment with ATO is administered intravenously at 0.15 mg/kg daily until bone marrow remission. Total dose should not exceed 60 doses and should be stopped at any time if substantial toxicity occurs. Consolidation treatment is given 3 to 6 weeks after completion of induction therapy, administered intravenously at a dose of 0.15 mg/kg daily for 25 doses over a period up to 5 weeks.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

First Line setting

Three randomized controlled trials met the eligibility criteria for this review. Lo-Coco 2013[1] evaluated the non-inferiority of ATO in combination with ATRA (n=77) in comparison to ATRA/chemotherapy (n=79) as an induction and consolidation treatment. Powell 2010[2] evaluated early stage consolidation with (n=244) or without ATO (n=237) monotherapy. Shen 2004[3] evaluated ATO (n=20), ATRA (n=20) and ATO/ATRA combination (n=21) as induction therapy. Most patient characteristics were well matched within and between trials in the Lo-Coco and Powell studies with no statistically significant differences in baseline characteristics between the study arms. However, the Powell study included low, intermediate and high risk patients as defined by their white blood cell counts while the Lo-Coco study included only low/intermediate risk patients. There were limitations in the Shen study in terms of the sample size, generalizability of the patient population, lack of information on the randomization and blinding and unclear reporting of results that created significant uncertainty in the comparability of Shen 2004 to the two other included studies.

Relapsed/Refractory setting

No randomized controlled trials comparing ATO with a relevant comparator were identified that met the eligibility criteria of this review. Eleven prospective studies were however identified and included in the systematic review, each incorporating ATO into the treatment of relapsed/refractory APL in different combinations with other agents and at different stages of treatment (e.g. induction, consolidation or both). One study (Wang 2004[4]) included both a prospective arm (ATO monotherapy) arm and a comparative historical cohort (ATRA). One study (Raffoux 2003[5]) was a randomized controlled trial that had ATO in both arms and thus did not

provide an appropriate comparison but was considered as a prospective cohorts for the purpose of this review. The remaining 9 studies were single arm, non-randomized, non-comparative studies. (Alimoghaddam 2011[6], Lazo 2003[7], , Niu 1999[8], Shen 2001[9], Shen 1997[10], Shigeno 2005[11], Soignet 2001[12], Soignet 1998[13], Yanada 2013[14]). In the Wang 2004 study some patients in the ATRA/ATO and ATO alone arm had received ATO containing treatment in the first line setting. In all other included relapsed/refractory studies, the previous first line treatment regimen of patients was either not reported or included an ATRA/chemotherapy containing regimen.

There was variability among the eleven included studies in terms of trial sample sizes (range 12[13] – 47[8]), population characteristics, variability in the treatment protocols (including variability in the number of consolidation cycles) and measurement of outcomes. As such heterogeneity between the trials made pooling of results from the relapse/refractory setting inappropriate and the ability to generalize results was difficult.

Although none of the included studies (first-line or relapse/refractory setting) were conducted solely in a pediatric population, many studies allowed for both children and adults to be included.

Efficacy

First Line

Event-free survival (EFS) was the primary endpoint in Lo-Coco and Powell studies. In the Lo-Coco study, the addition of ATO/ATRA to the induction and consolidation treatment resulted in EFS that was non-inferior (97% vs. 86%) to the ATO/ATRA vs. ATRA/chemotherapy arms, respectively, p<0.001, and possibly statistically superior to ATRA/Chemo (p=0.02)[1]. In the Powell study, the addition of ATO during early consolidation treatment also created superior 3 year event free survival rates of 80% versus 63% (p<0.001)[2]. Subgroup analysis for EFS in high risk (p=0.015), low/intermediate risk (p=0.0003) patients showed significant difference in EFS in favor of ATO arm. Shen 2004[3] did not report EFS.

While Lo-Coco did not report statistically significant improvements in disease free survival (DFS) rates for ATO when compared to the chemotherapy arm, Powell demonstrated a statistically significant improvement between the two treatment arms, 90% ATO versus 70% non-ATO, in early consolidation (p<0.001). Similar results were found in subgroup analysis of low/intermediate and high risk groups (p<0.001). There was no statistically significant difference between high risk and low/intermediate risk patient groups in the ATO consolidation arm indicating no difference in efficacy of regime between low risk and high risk cases. Although measured, DFS was not tested for superiority between treatment arms in Shen, 2004[3].

Relapsed/refractory

All trials reported complete remission (CR) as an endpoint. Although not reported in all studies, other outcomes included DFS, event free survival (EFS), overall survival (OS) and toxicity.

Complete remission rates ranged from 71% (Wang, 2004[4]) to 100% (Lazo, 2003[7]) and the median CR rate for all the studies was 85%. In the Wang study, which had a historical cohort comparator arm of ATRA alone, CR was 71% vs 20% in patients that received ATO/ATRA vs ATRA, respectively p<0.05[4]. The study also reported that there was no significant difference in the outcomes for patients that had previously failed ATO containing treatment regimens in the first line setting.

There was variability in the reporting of the other outcomes. Two year EFS was reported to be 17% in Shigeno 2005[11] and 5-year EFS was 65% in Yanada 2013[14]. Two-year DFS, as reported by 2 studies, was 46.6%- in Alimoghaddam 2011[6], and 54.6% in Niu 1999[8]. Overall survival results were also quite variable between studies with 2 year OS ranging from 56%-81.1% in three studies.

Quality of life was not reported in either first line or relapsed/refractory studies.

Harms

First line:

More deaths were reported in the chemotherapy arm than the ATO arm in the Lo-Coco study (7 vs 1 patients, respectively) with the most common causes of death being APL differentiation syndrome, hemorrhagic shock and bronchopneumonia[1] . Powell reported similar number of deaths in both arms however subgroup analysis by risk group showed that more deaths occurred in the high risk patients with 4%, 4% and 20% of deaths occurring in the low, intermediate and high risk groups, respectively[2]. Although no description was provided, four deaths were reported in Shen, 2004[3] during induction therapy (with 2 patients (10%) having died in the ATO arm), all of whom were attributed to intracerebral hemorrhage.

APL differentiation syndrome occurred in 37% of patients during induction in Powell and no difference in incidence was reported in Lo-Coco. Similarly, Powell reported QT prolongation in 16% vs 0 of patients in the ATRA-ATO arm vs. ATRA/Chemo arms, respectively, ($p<0.001$), while Lo-Coco reported 12 events (16%) in the ATO arm versus no events at all in either group ($P<0.001$).

In the Shen study, hyperleukocytosis appeared earlier in the combined therapy group, but the frequency of occurrence and the between group differences in level did not reach statistical significance[10].

Relapsed/Refractory setting

Deaths were reported in all studies ranging from 3%-41% of patients. Two deaths were reported to be due to APL differentiation syndrome. Shigeno 2005[11] reported more deaths than any of the other studies (41%) with the majority of deaths being due to stem cell transplant following remission (which are not usually counted in other studies) and deaths due to relapse during chemo/ATRA postremission therapy. In the Wang study, more patients died in the ATRA vs ATO/ATRA arm, 33.3% vs 7.4%, respectively $p>0.05$.

Two studies reported APL differentiation syndrome in 29% and 35% of patients[5, 6] while QT interval prolongation was reported in 3 studies occurring in a range of 17%-74% of patients [5, 11, 12, 15]. Five studies reported incidence of leukocytosis or hyperleukocytosis occurring in a range of 40%-55% of patients[8, 9, 11-13]. Wang 2004[4] reported that there was no significant difference in the main clinical and hematological characteristics or in the nature of the hyperleukocytosis among the ATRA and ATO/ATRA groups.

The most frequent toxicities resulting in dose modifications were neuropathy, cardiac toxicity, retinoic acid syndrome, APL differentiation and major organ dysfunction.

1.2.2 Additional Evidence

pCODR received input on arsenic trioxide from one patient advocacy group (Leukemia & Lymphoma Society of Canada, LLSC). Provincial Advisory Group input was obtained from

eight of nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR.

In addition, the following information is discussed as supporting information:

- A review of Thomas et al,2000[16] providing information on comparators in the relapsed/refractory indication setting.

1.2.3 Interpretation and Guidance

Burden of illness, and Need

Acute promyelocytic leukemia (APL) is a rare subtype of acute myelogenous leukemia accounting for 5 – 8% of cases of AML. With an estimated age adjusted incidence of 0.073 cases per 100,000 for the period 1993 – 2007, APL is a very uncommon disease[17]. With the advent of all trans-retinoic acid (ATRA) and initial remission rates achieved are quite high with 100% being achieved in some trials, and cure rates of up to 80%[18]. Relapse however occurs in roughly 20% of cases, and a small proportion of patients become unresponsive to treatment[19]. Due to the toxicity associated with current induction treatments there is significant interest in studying and developing less toxic treatment options of which arsenic trioxide is one. For example, long-term adverse effects of treatment with anthracyclines can include second cancers, cardiomyopathy and myelodysplasia.

Effectiveness

The efficacy of arsenic trioxide (ATO) in initial treatment of APL has been shown in two key studies, those of Lo-Coco[1] and Powell[2]. In the Lo-Coco study, results demonstrated a two-year event-free survival of 97% vs. 86% in the ATO and chemotherapy arms, respectively. The results in the ATO arm were non-inferior ($p<0.001$) and superior ($p=0.02$) to those in the chemotherapy arm[1]. Event-free survival was significantly better in the group that received ATO (80% vs. 63% at 3 years, $p<0.0001$) with benefit seen in all risk groups[2].

In the relapsed/refractory setting, despite limitations in the literature (majority of studies are small, single institution reports) overall results clearly show that ATO is active in relapsed and refractory APL. Complete remission rates in these reports range between 71 – 100%, with a median of 85%.

Safety

Although the treatment of APL is associated with several unique side effects (hyperleukocytosis and APL differentiation syndrome), appropriate vigilance and early treatment with cytoreduction or steroids can prevent severe consequences of these conditions. In general, the occurrence of these side effects in patients was acceptable for both indications in the included studies. Likewise, as APL is treated only in highly specialized centers the outcome of hyperleukocytosis and APL differentiation syndrome tend to be quite good. ATO is also associated with prolonged QT interval; this can however be managed reasonably by treating oncologists.

1.3 Conclusions

The Clinical Guidance Panel concluded that there is net overall clinical benefit to using ATO in induction and/or consolidation for treatment of low-, intermediate- and high-risk APL with PML-RARA fusion. This conclusion is based on the results of two high quality comparative trials

demonstrating superior survival when this disease is treated with ATO. The safety profile is favourable and comparable to current treatments. The resources required to treat APL with ATO are similar to those required to treat other subtypes of AML and are likely to have only a small impact due to the low burden of the disease. Incorporation of ATO into front-line treatment may minimize late effects of treating this disease with anthracyclines, including second cancers, cardiomyopathy and myelodysplasia. Despite the lack of pediatric trials the CGP considered that given similar pathogenesis the results of the adult studies should be generalizable to children. It would be reasonable to offer arsenic trioxide to children with APL and PML-RARA fusion.

Despite the lack of randomized trials in this area the Clinical Guidance Panel concluded that there is net overall clinical benefit to using ATO for reinduction of relapsed or refractory APL patients. This conclusion is based on the unmet medical need in this population and the activity of ATO in relapsed APL demonstrated in multiple single-arm reports. The panel considered that this was especially the case for patients who had not received ATO previously but that ATO should not be withheld from patients who relapse after ATO-containing regimens, particularly those who relapse late. Despite the lack of pediatric trials the CGP considered that given similar pathogenesis it would be reasonable to offer arsenic trioxide to children with relapsed APL and PML-RARA fusion.

2 CLINICAL GUIDANCE

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding arsenic trioxide (Trisenox) for acute promyelocytic leukemia (APL). The Clinical Guidance Report is one source of information that is considered in the pERC Deliberative Framework. The pERC Deliberative *Framework* is available on the pCODR website,www.pcodr.ca.

This Clinical Guidance is based on: a systematic review of the literature regarding arsenic trioxide (Trisenox) conducted by the Leukemia Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; and supplemental issues relevant to the implementation of a funding decision.

The systematic review and supplemental issues are fully reported in Sections 6 and 7. Background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input on arsenic trioxide (Trisenox) and a summary of submitted Provincial Advisory Group Input on arsenic trioxide (Trisenox) are provided in Sections 3, 4 and 5 respectively.

2.1 Context for the Clinical Guidance

2.1.1 Introduction

Acute Promyelocytic Leukemia (APL) is a sub-type of Acute Myeloid Leukemia and is characterized by the unique chromosomal translocation t(15;17) that results in the formation of the PML-RAR alpha fusion protein. With an estimated age adjusted incidence of 0.073 cases per 100,000 for the period 1993 – 2007, APL is a rare disease[17]. Acute promyelocytic leukemia was once a rapidly fatal form of leukemia but that has changed due to the advent of all trans-retinoic acid (ATRA) and initial remission rates achieved are quite high with 100% being achieved in some trials, and cure rates of up to 80%[18]. Relapse occurs in roughly 20% of cases, and a small proportion of patients become unresponsive to treatment[19]. Patients with APL who have been treated with ATRA/Chemotherapy experience hematologic toxicities. These adverse events are particularly problematic in high risk cases, where high risk is defined not only by white blood cell count, but also by patient age and performance status. Because of the toxicity associated with current induction treatment standard there is significant interest in studying and developing less toxic treatment options of which arsenic trioxide is one.

Arsenic trioxide causes morphological changes and DNA fragmentation characteristic of apoptosis in NB4 human PML cells in vitro. Arsenic trioxide also causes damage or degradation of the fusion protein PML-RARα. The combination of ATRA and ATO has been shown to produce synergistic effects on cell apoptosis in patients with APL and been shown to be very successful, producing positive treatment outcomes as both combination therapy and monotherapy. In the U.S., Europe, and Canada Arsenic Trioxide (ATO) has been indicated for use in induction of remission and consolidation in patients with APL who are refractory to, or have relapsed from, retinoid and anthracycline chemotherapy and whose APL is characterized by presence of the t(15;17) translocation of PML/RAR-alpha gene expression (HC/EMA/FDA)[20-22]. More recently, studies have been conducted with the intention of reviewing the use of arsenic trioxide in the frontline setting[1-3].

2.1.2 Objectives and Scope of pCODR Review

To evaluate the effectiveness of Arsenic Trioxide (ATO), as monotherapy or in combination with ATRA and/or other chemotherapy agents, on patient outcomes compared with appropriate comparators in treatment of patients and associated subgroups with:

- Previously untreated Acute Promyelocytic Leukemia.
- Relapsed/Refractory Acute Promyelocytic Leukemia.

For the relapsed/refractory indication, non-randomised studies were also included in the systematic review. Therefore studies identified evaluating the use of ATO did not need a comparator arm.

2.1.3 Highlights of Evidence in the Systematic Review

This section describes highlights of evidence in the systematic review. Refer to section 2.2 for the clinical interpretation of this evidence and section 6 for more details of the systematic review.

First Line Setting

Three randomized trials met the eligibility criteria and form the evidence base for this review. Each trial incorporated ATO into treatment in different treatment phases, and in different combinations with other agents. Combinations included: Induction and consolidation in combination with ATRA and chemotherapy; early stage consolidation as monotherapy, prior to chemotherapy; Induction therapy as both monotherapy as well as in combination with ATRA.

Induction & Consolidation (Lo-Coco, 2013):
Lo-Coco, 2013[1] is a non-inferiority trial designed to determine whether arsenic trioxide is not inferior, to ATRA/Chemotherapy for front line (induction & consolidation) treatment of APL. Primary endpoint was 2 yr. event free survival. Secondary endpoints included overall survival, disease free survival, APL differentiation syndrome, and both hematologic and non-hematologic toxicity. A total of 162 patients were enrolled, 156 were evaluable and randomized to treatment. Seventy seven patients were randomized to ATRA/ATO and 79 patients were randomized to ATRA/chemo. Age, gender, WBC counts, and platelet counts were divided evenly between arms with no statistical difference in baseline characteristics between the study arms.

Two year event free survival was 97% in the ATRA–arsenic trioxide group versus 86% in the ATRA–chemotherapy group p<0.001 for non-inferiority). Two year overall survival rates were 99% in the ATRA–arsenic trioxide group and 91% in the ATRA–chemotherapy group (p = 0.02). Two year disease free survival rate was 97% in the ATRA–arsenic trioxide group and 90% in the ATRA–chemotherapy group (p = 0.11). There were 26 episodes of hematologic toxicity in the ATRA/ATO group versus 59 episodes in the ATRA/Chemo arm (p<0.001). 63% of patients in the ATRA/ATO arm and 6% in the ATRA/Chemo arm experienced grade 3 or 4 hepatic toxic effects (p<0.001), but all resolved with discontinuation. Prolonged QT interval occurred in 12 patients in the ATRA/ATO group and in no patients in the ATRA/Chemo group (p<0.001).

Because of the study design and the uncertainty related to randomization and concealment procedures because they are not reported, there is moderate chance that bias has been introduced into study results. It should also be noted that results can only

be generalised to the population included in this study which is low-intermediate risk APL patients as defined in the study.

Early Consolidation (Powell, 2010):
Powell, 2010[2] is a 2-arm randomized trial examining the use of ATO in early consolidation treatment (following achievement of complete remission (CR) in induction and prior to chemo in consolidation). Primary endpoint was 3 yr. event free survival and secondary endpoints included 3 yr. disease free survival as well as toxicity. A total of 481 patients were enrolled in the study with 237 randomized to the Non-ATO treatment arm and 244 randomized to the ATO treatment arm. Patient characteristics were well matched in terms of age, gender, and risk. There were no statistical differences in baseline characteristics between the study arms.

Three year event free survival was 80% versus 63% ($p<0.0001$), disease-free survival was 90% versus 70% ($p<0.0001$), and 86% versus 81% in the standard arm ($p=.07$) for ATO and non/ATO arms respectively. No grade 3 or 4 cardiac toxicities due to QT prolongation were reported on the ATO arm, while APL differentiation syndrome reported in 37% of cases in induction phase, and none in consolidation. Reported hematologic adverse events due to consolidation were 16% grade 3 and 67% grade 4 on the standard arm, and 21% grade 3 and 54% grade 4 on the As_2O_3-containing arm. Non-hematologic adverse events due to consolidation treatments were 30% grade 3 and 5% grade 4 for the standard arm, and 41% grade 3 and 5% grade 4 for the As_2O_3-containing arm.

Validity and reliability from this trial may be problematic due to the fact that it is an open label trial and uncertainty exists about whether blinding was used for participants and investigators. Adding to this is the fact that no detailed description of the randomization procedures used was available. Likelihood of bias is low but does exist based upon these limitations.

Induction (Shen, 2004):
Shen, 2004[3] is a 3-arm, randomized clinical trial and is the last trial included in this review. This trial evaluated the use of ATO in induction therapy, as monotherapy, as well as in combination with ATRA. Primary endpoints in this study were identified as achievement of complete remission and disease free survival. A total of 61 patients were enrolled in the study with 20 randomized to the ATRA treatment arm, 20 randomized to the ATO treatment arm, and 21 randomized to the ATRA/ATO treatment arm. Median age of patients was 30.5 yrs., 39.5 yrs., and 34 yrs. for the ATRA, ATO, and ATRA/ATO treatment groups correspondingly.

White blood cell counts were stratified by <2 $X10^9$/Litre, 2-10 $X10^9$/Litre, or >10 $X10^9$/Litre. Patients in the ATRA group were 30%, 50%, and 20%, for those categories respectively. Median hemoglobin and range as well as median platelet count were reported for all arms. Complete remission rate was not statistically different between groups, but time to CR was with suggested superiority for those in combined therapy. Median DFS was 13 months, 16 months, and 20 months for groups ATRA, ATO, and ATRA/ATO groups respectively.

Several limitations were noted in this trial. No descriptions of blinding and randomization were given. Sample size was very low, and there was no description of sample size calculation and power level for which results can be interpreted. Further, population was limited by race, and age characteristics may have been skewed in favor of arsenic trioxide treatment based upon the consideration that older patients are higher risk for co-

morbidities and death. DFS results were not reported in standard fashion with no explanation of calculation methods.

Relapse/Refractory Setting

No randomized trials were identified that met the eligibility criteria of this review. Eleven studies were identified and included in the systematic review. Each study incorporated ATO into treatment of relapsed/refractory APL in different combinations with other agents. Treatment schedules were different and ATO was incorporated into different phases by trial.

Alimoghaddam, 2011 is a single arm, non-randomized clinical trial that examined the use of ATO as salvage therapy in 31 previously treated APL patients who relapsed. Relapse was confirmed for all patients with morphology and RT-PCR. Patients were treated until complete remission was achieved and followed with consolidation therapy. Primary endpoints included CR, DFS, OS, and secondary endpoints included toxicity. Complete remission was 77.4%. 2 yr DFS and 2 yr OS was 54.6% and 81.1% respectively. Median number of days to CR was 30 and there were four patient deaths resulting from APL differentiation, intracranial hemorrhage, and disease progression. APL differentiation was seen in 9 patients (29%), liver dysfunction in 3 patients and mild pericardial and pleural effusion in one case. The main limitation of this trial was the single race population, and the small sample size.

Lazo, 2003[7] is a single arm, non-randomized prospective cohort trial that examined the use of ATO monotherapy as induction relapse therapy in 12 previously treated APL patients who have relapsed. Primary endpoints included CR, molecular remission, and neuropathy. Molecular remission was seen in 70% of patients. Side effects were mild and included headache, rash, GI pain, and fluid retention. Two patients developed peripheral neuropathy. The main limitation associated with this trial is the sample size.

Niu, 1999[8] is a single arm, non-randomized prospective cohort trial that examined the use of ATO as induction relapse therapy in 47 previously treated APL patients in relapse. Patients were treated with ATO as a single agent. Primary endpoints included CR, and DFS.
A complete remission rate of 85.1% was found in the ATO treatment group. Seven cases of hepatic toxicity, mild liver toxicity in one third of patients, and two deaths were reported. Median DFS was 17 months and estimated 1 & 2 yr. DFS was 63.6% & 41.6%. The main drawback of this study was the small sample size.

Raffoux, 2003[5] is a double arm, randomized controlled trial that examined the use of ATO versus ATO and ATRA as induction relapse therapy in 20 previously treated APL patients who have relapsed. Patients were treated with ATO as a single agent or in combination with ATRA. Primary endpoints included time to CR, while secondary objectives included safety and molecular response. A complete remission rate of 80% was found after one treatment with ATO with or without ATRA. Two patients died in induction therapy due to septic shock with seizures, and APL differentiation syndrome. Weight gain was seen in 60% of cases, hypolakemia in 35%, and all of hyperglycemia, nausea/vomiting and QT prolongation in 25% of patients. Diarrhea, peripheral neuropathy, deep venous thrombosis, and differentiation syndrome were also reported in 20%, 10%, 10%, and 35% of patients. Evidence from this study is taken from the prospective cohort being treated with ATO alone. The comparative metrics reported are not used as part of evidence because they reflect results of a comparison that is not valid for our research objective. No statistical difference in frequency of events was seen between arms. The main

limitation associated with this study is the small sample size and the lack of information on methods pertaining to randomization and allocation.

Shen, 2001[9] is a single arm, non-randomized prospective cohort study that examined the use of ATO as induction relapse therapy in 20 previously treated APL patients in relapse. This was compared with a historical cohort, conventional ATO dose group. Primary endpoints included hepatic toxic, APL differentiation, 2 yr. OS, and 2 yr. DFS. In the low dose group there was two patient deaths due to intracranial hemorrhage, 20% of patients had impaired hepatic function, oral ulcer (10%), skin rash (10%), and hyperleukocytosis in 40% of patients from the low dose treatment group. Four patient deaths due to intracranial hemorrhage were reported in the conventional dose treatment group along with 31.9% of cases with hepatic dysfunction, skin rash (60%), GI disturbance (25%), cardiotoxicity (40%), facial edema (25%), and neurotoxicity (5%). The main limitation associated with this study is the small sample size. Comparisons made with historic cohort have limited validity compared with RCTs due to uncertainty surrounding between arm comparisons.

Shen, 1997[10] is a single arm, non-randomized prospective cohort study that examined the use of ATO as induction relapse therapy in 15 previously treated APL patients in relapse. Patients were treated with ATO as a single agent. Main study endpoints included complete remission and toxic events. The study reported a 90% complete remission rate, with a median time to remission of 38 days, following induction with ATO. Skin eruptions (27%), headache (6.7%), EKG change (13%), nausea (27%), liver dysfunction (47%), enlargement of salivary gland (7%), thyrophyma without thyroidism (7%), arthralgia or musculogia (13%), teeth ache (13%), oral ulcer (7%), and hemorrhage of teeth/nose/skin (13%) were also reported. The main limitation with this study is the small sample size.

Shigeno, 2005[11] is a single arm, non-randomized prospective cohort study that examined the use of ATO as induction relapse therapy in 34 previously treated APL patients in relapse. Patients were treated with ATO as a single agent. All patients had been previously treated with ATRA. Patients were evaluated for CR, cardiac toxicities, APL differentiation, 2 yr. OS, 2 yr. EFS, liver dysfunction, and neuropathy. A complete remission rate of 91% complete was reported with a median time to CR of 46 days. APL differentiation syndrome was found in 8 patients. Estimated 2 yr overall survival and event free survival rates were 56% and 17%. Other adverse events included prolongation of the QT interval (74%), hyerleukocytosis (32%), severe neutropenia, anemia, and thrombocytopenia in 97%, 68% and 62% of patients. The main limitation associated with this study is the small sample size and lack of generalizability.

Soignet, 2001[12] is a single arm, non-randomized prospective cohort trial that examined the use of ATO as induction relapse therapy in 40 previously treated APL patients in relapse. Patients were treated with ATO monotherapy. Consolidation therapy as well as ATO maintenance was provided in some cases. Primary endpoints included CR, cardiac toxicities, APL differentiation, 18 month OS and RFS, and leukocytosis. Two patient deaths were reported following last study treatment and were related to intravascular coagulopathy and hemorrhage. Eighty five percent of patients achieved complete remission and a median time to bone marrow remission of 35 days. Eighteen month overall survival and relapse free survival rates were 66% and 56%. Sixty eight percent of patients had a grade 3 or 4 adverse event, 40% of patients showed ECG abnormalities, 58% of patients had adverse events related to coagulopathy, 48% of patients had severe adverse events. The main limitation associated with this study is the small sample size.

Soignet, 1998[13] is a single arm, non-randomized prospective cohort trial that evaluated the use of ATO as induction relapse therapy in 12 previously treated APL patients in relapse. Patients were treated with ATO monotherapy until leukemic cells were eliminated from bone marrow. Primary endpoints included CR, adverse events, and gene expression. One early phase patient death due to intracranial hemorrhage was reported. Severe adverse events included pulmonary hemorrhage, renal failure, sepsis, graft-versus host disease, nonspecific pulmonary infiltrates, retinoic acid syndrome, leukocytosis, and hypotension. Other adverse reactions were reported. The main limitation associated with this study is the small sample size.

Wang, 2004[4] is a comparison of one single arm, non-randomized, single institution, prospective cohort study evaluating the use of ATO as induction relapse therapy with a prospective cohort and a retrospective cohort. Patients were treated with ATO in combination with ATRA. Comparison was with a prospective cohort treated with ATO alone, as well as a retrospective cohort treated with ATRA alone. Some patients in the ATO/ATRA and prospective ATO alone groups had previously failed ATO containing regimens in the first line setting. Primary endpoints included CR, mortality, and toxic side effects. Complete response was reported in 71% of patients. There was no significant differences in outcomes among patients that had received prior ATO in the first line setting compared to those that did not. Three patient deaths were reported during the early induction phase of treatment. All patient deaths were related to disseminated intravascular coagulation. The patterns of toxic effects among the three groups of relapsed patients were not described in detail, but include: in general, treatment with ATRA alone caused the highest incidence of pleural and peritoneal effusion, DIC, skin reactions, headache, dyspnoea and bone ache as observed in newly-diagnosed patients; ATO alone caused a high incidence of hepatic injury; and combined use of LD-ATRA with ATO however, did not further enhance toxic side-effects as compared to ATO alone. The main limitation associated with this study is the small sample size. Also, comparisons made with historic cohort have limited validity compared with RCTs due to uncertainty surrounding between arm comparisons.

Yanada, 2013[14] is a single arm, non-randomized prospective cohort trial that evaluated the use of ATO as induction and consolidation therapy in 35 previously treated APL patients in relapse. Patients were treated with ATO alone followed by hematopoietic cell transplantation. Main endpoints included CR, 5yr OS & EFS. One early phase death was reported, resulting from intracranial hemorrhage. Complete response was reported in 81% of cases, with 9 cases achieving molecular remission. Five year EFS, OS, and failure free survival rates were estimated to be 65%, 77% and 59%. Other adverse events during induction were skin rash, QT prolongation, and QT prolongation accompanied by frequent premature ventricular contraction. The main limitation associated with this study is the small sample size.

In summary complete remission rates, survival, and toxicity data support the use of ATO in the relapse/refractory setting. Sample sizes and between study population and treatment differences, including variability in the number of consolidation treatment cycles, make generalizability of results difficult. There was limited discussion in these studies regarding the use of ATO in patients who have no other treatment alternatives, an important consideration in the use of ATO in relapse/refractory setting.

2.1.4 Comparison with Other Literature

Relevant literature identified jointly by the pCODR Clinical Guidance Panel and Methods Team and providing supporting information to the systematic review is summarized below. This information has not been systematically reviewed.

A review of methods used to establish comparator arm treatment algorithm for the economic evaluation in the relapsed/refractory indication setting (see pCODR Economic Guidance Report) was undertaken. The study, "*Treatment of relapsing acute promyelocytic leukemia by all-trans retinoic acid therapy followed by timed sequential chemotherapy and stem cell transplantation*"[16] was used by investigators to create the comparative arm. This is a single arm prospective trial. Relapsed patients have had confirmed diagnosis of APL by presence of t(15;17) translocation and/or PML/RARa gene rearrangement. Three different groups were treated with different frontline regimes. Relapse treatment included an ATRA & chemotherapy based induction with SCT as consolidation. Patients ineligible for auto/Allo graft were treated with chemotherapy maintenance. Overall, 90% of patients made it to CR, severe infection developed in 54%, 11 patients were treated with allogenic BMT with median DFS of only 8.2 months, and only 22 were allografted.

Limitations of this study include invalid comparisons due to i) differing post remission therapies, and ii) treatment allocation that is not randomized. Generalizability of results for use as comparator should be interpreted with attention.

2.1.5 Summary of Supplemental Questions

No supplemental questions were addressed in this review.

2.1.6 Other Considerations

See Section 4 and Section 5 for a complete summary of patient advocacy group input and Provincial Advisory Group (PAG) Input, respectively.

Patient Advocacy Group Input

From a patient perspective, respondents would like to see an effective treatment for APL with fewer long-term side effects. LLSC reported that the majority of patient with APL who make it through their initial days of diagnosis and treatment are successfully cured of the disease. While some respondents treated with arsenic trioxide may experience some nausea, it was reported to be much milder than experiences with chemotherapy, and respondents felt that it could be controlled with supportive therapies. Respondents believe that it is highly important a patient is treated with the right medications to ensure remission.

PAG Input

Input on Arsenic trioxide (Trisenox) for APL was obtained from eight of the nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. From the PAG perspective, the main enabler is the unmet need for the relapsed/refractory APL patients. Barriers to implementation include the daily one-hour intravenous infusions and monitoring for serious events listed in the black box warning. The daily administrations require additional chair time or hospital admission and presents resource challenges for smaller clinics and hospitals. Monitoring and treating serious adverse events also requires additional resources.

Other

Oral Arsenic: The pCODR systematic review focussed on the use of intravenously administered arsenic trioxide compared to ATRA/Chemotherapy. Intravenous ATO was also used in all of the labels and indications identified for Health Canada, the FDA and EMA. Due to the need for intravenous delivery which is an in-patient procedure, there is desire to determine whether oral arsenic treatment is possible which could eliminate costs and improve patient comfort. Although not systematically reviewed, the results of one trial examining the efficacy of intravenous arsenic trioxide versus an oral form, tetra-arsenic tetra sulfide, suggest the oral form may be non-inferior to the liquid ATO. Currently, there are no comparative studies analysing the efficacy of oral arsenic compared to ATRA/Chemotherapy.

Arsenic trioxide currently has a Health Canada indication for induction of remission and consolidation in patients with acute promyelocytic leukemia (APL), which is refractory to or has relapsed from retinoid and anthracycline therapy, and whose APL is characterized by the presence of the t(15;17) translocation or promyelocytic leukemia-retinoic-acid-receptor alpha (PML-RARα) gene expression[53]. The Health Canada product monograph discusses use in geriatric populations as well as pediatric populations and also indicates that it should be administered under supervision of physician who is experienced in management of patients with acute leukemia. Warnings and precautions in the Health Canada product monograph included APL differentiation syndrome, Acute Cardiac Toxicities[53]. The FDA and EMA indications are similar to the Health Canada indication. Additional risks associated with arsenic trioxide listed on the EMA website[22] as also include hyperglycaemia (high blood glucose levels), hypomagnesaemia (low blood magnesium levels), hypokalaemia (low blood potassium levels), paraesthesia (unusual sensations like pins and needles), dizziness, headache, tachycardia (rapid heartbeat), dyspnea (difficulty breathing), diarrhea, vomiting, nausea (feeling sick), pruritus (itching), rash, myalgia (muscle pain),pyrexia (fever), pain, fatigue (tiredness), oedema (swelling),and increased levels of alanine aminotransferase and aspartate aminotransferase (liver enzymes).

2.2 Interpretation and Guidance

Burden of Illness and Need

Acute promyelocytic leukemia (APL) is a rare subtype of acute myelogenous leukemia accounting for 5 – 8% of cases of AML. The hallmark feature of this disease clinically is a severe bleeding disorder, which occurs as a result of disease-related thrombocytopenia and intravascular coagulation. Pathologically the disease features a balanced translocation between chromosomes 15 and 17, which creates a fusion gene combining a portion of the PML locus and the retinoic acid receptor alpha subunit (PML-RARA). This fusion protein reversibly inhibits maturation of myeloid cells at the promyelocyte stage and accumulation of abnormal promyelocytes within the bone marrow. Subtypes of APL featuring alternative translocations (t(5; 17) and t(11; 17)) exist but are not influenced by retinoids and arsenic trioxide and are not considered in these recommendations.

Current treatment strategies for APL combine all-trans retinoic acid (ATRA) with anthracyclines in induction and consolidation. Selected high-risk patients may also benefit from the addition of Cytarabine. Early side effects of this regimen include nausea, cytopenias, hair loss, fatigue, dry mucous membranes and skin and potential normal-pressure hydrocephalus. APL differentiation syndrome may occur, which causes fluid retention, pulmonary edema and hypoxia. Late effects include cardiomyopathy and second myeloid malignancies such as therapy-related AML. Strategies

that combine ATRA and anthracycline chemotherapy result in induction failure rates of 6-10% with a further 10-20% of patients relapsing within 6 years. Patients with APL have indicated that they are looking for treatment with fewer early and late side effects. Although many patients who fail front-line therapy respond to arsenic trioxide on retreatment patients place a high value on successful up-front therapy and prefer treatments with the highest initial likelihood of cure.

Efficacy

The efficacy of arsenic trioxide (ATO) in initial treatment of APL has been shown in two key studies, those of Lo-Coco[1] and Powell[2]. LoCoco[1] reported the results of a phase 3, multicenter trial comparing ATRA plus chemotherapy with ATRA plus ATO in patients with low- and intermediate-risk APL. ATO was given during induction and consolidation. Using a non-inferiority design the authors were able to demonstrate a two-year event-free survival of 97% vs. 86% in the ATO and chemotherapy arms, respectively. The results in the ATO arm were non-inferior ($p<0.001$) and superior ($p=0.02$) to those in the chemotherapy arm. Powell[2] randomized 481 patients with untreated APL to standard induction and consolidation or standard induction and consolidation plus two 25-day courses of ATO between induction and consolidation. Patients in this study had low-, intermediate- and high-risk APL. Event-free survival was significantly better in the group that received ATO (80% vs. 63% at 3 years, $p<0.0001$). Patients in all risk groups benefited from ATO.

The Systematic Review identified 11 unique studies using ATO in patients with relapsed or refractory APL. The majority of these are small, single institution reports describing local experience in small numbers of patients. Single-arm reports describe a median of 28 (range 12 – 47) patients with a range of mainly short-term outcome measures including reinduction success, toxicity and short term survival. Post-reinduction therapy is often poorly described in these reports. One prospective comparative study randomized relapsed APL patients to ATO vs. ATO plus ATRA, making it unsuitable to determine the role of ATO relative to ATRA in this setting. Despite these limitations this literature clearly shows that ATO is active in relapsed and refractory APL. Complete remission rates in these reports range between 71 – 100%, with a median of 85%. Subsequent treatment, either further rounds of consolidation, application of novel agents such as gemtuzumab ozogamicin or autologous or allogeneic stem cell transplantation, was applied to maintain these remissions. Given relapsed APL is very uncommon it is unlikely that large randomized trials will be completed.

The Provincial Advisory Group has identified the lack of standard treatment for patients with relapsed APL as an important issue to resolve and indicate that ATO could meet this need.

Safety

The treatment of APL is associated with several unique side effects. These include hyperleukocytosis and APL differentiation syndrome, both of which occur with ATRA-chemotherapy combinations but seem to be more frequent when ATRA-ATO is used. Appropriate vigilance and early treatment with cytoreduction or steroids are necessary to prevent severe consequences of these conditions. As APL is treated only in highly specialized centers the outcome of hyperleukocytosis and APL differentiation syndrome tend to be quite good. ATO may also prolong the cardiac repolarization time (the QT interval). This can be managed by carefully monitoring and replacing potassium and magnesium, serial monitoring of the QTc interval by ECG and avoiding medications that might compound QTc prolongation.

Increased resource use to treat patients with APL is likely to be seen if ATO is adopted in the front-line setting. This includes increased outpatient chair time and requirement for treatment on

weekends during consolidation as identified by the Provincial Advisory Group. This resource use may be partially offset by a reduced utilization ATO and stem cell transplantation in the relapsed setting. Other patients with AML receive as many as four cycles of post-induction therapy and consequently may spend as many as twenty weeks as hospital inpatients during their initial treatment. While the treatment of APL with ATO may place additional burdens on outpatient resources it is likely less of a burden on the health care system as a whole than other AML subtypes.

2.3 Conclusions

The Clinical Guidance Panel concluded that there is net overall clinical benefit to using ATO in induction and/or consolidation for treatment of low-, intermediate- and high-risk APL with PML-RARA fusion. This conclusion is based on the results of two high quality comparative trials demonstrating superior survival when this disease is treated with ATO. The safety profile is favourable and comparable to current treatments. The resources required to treat APL with ATO are similar to those required to treat other subtypes of AML and are likely to have only a small impact due to the low burden of the disease. Incorporation of ATO into front-line treatment may minimize late effects of treating this disease with anthracyclines, including second cancers, cardiomyopathy and myelodysplasia. Despite the lack of pediatric trials the CGP considered that given similar pathogenesis the results of the adult studies should be generalizable to children. It would be reasonable to offer arsenic trioxide to children with APL and PML-RARA fusion.

Despite the lack of randomized trials in this area the Clinical Guidance Panel concluded that there is net overall clinical benefit to using ATO for reinduction of relapsed or refractory APL patients. This conclusion is based on the unmet medical need in this population and the activity of ATO in relapsed APL demonstrated in multiple single-arm reports. The panel considered that this was especially the case for patients who had not received ATO previously but that ATO should not be withheld from patients who relapse after ATO-containing regimens, particularly those who relapse late. Despite the lack of pediatric trials the CGP considered that given similar pathogenesis it would be reasonable to offer arsenic trioxide to children with relapsed APL and PML-RARA fusion.

3 BACKGROUND CLINICAL INFORMATION

This section was prepared by the pCODR Leukemia Clinical Guidance Panel. It is not based on a systematic review of the relevant literature.

3.1 Description of the Condition

Acute promyelocytic leukemia (APL) is a subtype of acute myeloid leukemia (AML) with unique biologic and clinical features. Most patients are young, present with leukopenia, and exhibit a coagulopathy, which is the most notorious and potentially lethal manifestation of the disease. With initiation of treatment, however, the condition is highly curable. The cells from almost all patients have a balanced reciprocal translocation between chromosomes 15 and 17, which generates a fusion transcript joining the *PML* (promyelocyte) and *RAR*-alpha (retinoic acid receptor-alpha) genes. Leukemic promyelocytes have the unique ability to undergo differentiation with exposure to retinoic acid and both differentiation and apoptosis with exposure to arsenic trioxide (ATO). The disease is relatively uncommon in adults, accounting for only 10% of the adults diagnosed with AML in the United States each year[23]. Currently, there are 600-800 estimated new cases per year in the US[24]. In Canada, an extrapolation of the US data would suggest an incidence of 60-80 new cases per year.

3.2 Accepted Clinical Practice

Several international studies in the last 2 decades have established what is now the standard approach to the patient with newly diagnosed APL. The European APL group demonstrated that ATRA plus chemotherapy (daunorubicin and Ara-C) is superior to sequential ATRA followed by chemotherapy. The Gruppo Italiano Malattie EMatologiche dell'Adulto (GIMEMA) Italian Cooperative Group demonstrated excellent outcomes when ATRA was combined with idarubicin alone for induction. The North American Intergroup study showed a benefit to maintenance therapy with ATRA given every other week. The Programa Espanol de Tratamientos en Hematología (PETHEMA) Spanish Cooperative Group omitted Ara-C from both induction and consolidation and continued to demonstrate excellent outcomes.

Therefore, ATRA plus anthracyclines either alone or with Ara-C for induction is the current standard of care. For patients not participating on a clinical trial, ATRA and either daunorubicin (with or without Ara-C) or idarubicin can be given because there is no clear advantage of one anthracycline over the other. Idarubicin may result in a longer period of myelosuppression in some patients. Stem cell growth factors are not routinely administered in induction during the neutropenic period unless there is a documented life-threatening infection or signs or symptoms of sepsis.

The treatment of patients with APL represents a true emergency primarily because of bleeding, which continues to represent a major cause of early death. Once the diagnosis is even suspected on the basis of clinical findings and the peripheral blood smear (without waiting for a bone marrow examination), and before the diagnosis is confirmed by cytogenetic or molecular studies, ATRA should be started at the standard dose of 45 mg/m^2 per day in divided doses to prevent/treat the coagulopathy and to initiate induction therapy. Patients with WBC <10,000 initiate chemotherapy a few days later (i.e. daunorubicin on day 6). Patients with WBC >10 000 (high-risk disease) are at risk of further leukocytosis and exacerbation of the coagulopathy when ATRA is administered alone, along with the development of the APL differentiation syndrome`. APL differentiation syndrome occurs in up to 25% of patients early after initiation of ATRA or differentiation therapy[23]. The etiology is not clearly understood although an inflammatory cytokine release associated with ATRA (or ATO)-treated APL cells has been invoked. The syndrome is characterized by fever, weight gain, leukocytosis, respiratory distress and pulmonary infiltrates,

pleural and pericardial effusions, and renal failure. Given the associated risk of baseline WBC >10,000, patients who present with this high-risk feature should receive ATRA plus chemotherapy concurrently. Those who manifest signs of APL syndrome are further managed with steroids (i.e. dexamethasone 10 mg IV BID x at least 3 days). Additional supportive care measures are essential during the first few days of therapy in APL. Clinical bleeding, profound thrombocytopenia, and fibrinogen depletion are characteristic. Platelet and cryoprecipitate transfusions are routinely required to decrease the risk of fatal bleeding. Apart from these specific measures, general supportive care aspects including the use of antibiotics, stem cell growth factors, prevention of tumor lysis syndrome, and transfusions (once the coagulopathy is under control), do not differ from those applied in patients with other subtypes of AML.

Although current strategies using ATRA plus anthracycline-based chemotherapy lead to cures in the majority of patients with newly diagnosed APL, there are some potential long-term sequelae. These include the potential for relapse in around 20% of patients[19], second malignancies, including myelodysplastic syndromes, and delayed cardiomyopathy. New strategies that incorporate arsenic trioxide (ATO) early in the treatment of the disease possibly may prevent such complications.

ATO is the single most active agent in APL. Its mechanisms include direct degradation of the PML-RAR-alpha fusion transcript, with resulting transcription of RAR-alpha target genes leading to apparent differentiation as well as growth arrest of leukemia- initiating cells by apoptosis or loss of self-renewal. ATO also appears to release cytochrome C from the mitochondria, leading to caspase activation, which itself leads to apoptosis and synergy with retinoic acid in initiating leukemia cell loss.

ATO is being positioned for patients with newly diagnosed APL (in combination with ATRA) and in patients with relapsed/refractory disease. Previous evidence-based guidelines in APL (European Leukemia Net and NCCN) were produced prior to randomized evidence in support of ATO and ATRA combination therapy. As such, those recommendations were to consider the combination as an alternative therapy to ATRA + chemotherapy, especially in those with intolerance to anthracyclines or in countries in which arsenic-based therapies were less costly than chemotherapy. Following the randomized studies of ATO and ATRA in induction and consolidation for first-line APL, it is likely that this combination is being positioned to replace the current standard of ATRA + chemotherapy. ATO is dosed at 0.15mg/kg/day until CR with a maximum of 60 doses during induction with an additional 8-10 weeks of dosing in consolidation.

In the relapsed setting, ATO single agent therapy is a recommended therapy in all current evidence-based guidelines. No other treatment is currently approved in Canada. Prior to the availability of ATO, patients received ATRA and chemotherapy for re-induction followed by further chemotherapy consolidation with or without stem cell transplantation. If arsenic were contraindicated or ineffective, a reasonable regimen would include ATRA, amsacrine, and cytarabine. Otherwise, ATO would be recommended at 0.15mg/kg/day until CR with a maximum of 60 doses during induction and another 25 days in consolidation would be recommended.

3.3 Evidence-Based Considerations for a Funding Population

The disease is relatively uncommon in adults, accounting for only 10% of the approximately 13 400 adults diagnosed with AML in the United States each year. In Canada, an estimated 60-80 adults are diagnosed each year. Its incidence increases steadily during the teen years, reaches a plateau during early adulthood, and remains constant until it decreases after age 60 years. There is also an evolving literature regarding APL arising as a complication of previous exposure to chemotherapy (particularly drugs targeting topoisomerase II) or radiotherapy.

In Canada, there are no publications documenting the current usage of ATO for APL.

Several laboratory techniques can be performed to definitively confirm the diagnosis of APL. Conventional cytogenetics are highly specific and can detect variant translocations and should be obtained in every patient with suspected APL. Reverse transcriptase polymerase chain reaction (RT-PCR) for the PML-RAR-alpha fusion transcript is also routinely obtained, and has the advantage of successfully diagnosing APL in leukopenic patients. The disadvantages of RT-PCR include possible contamination, artifacts that might lead to a false-positive test, and a 48-hour turnaround time. Following induction and consolidation therapy, RT-PCR of bone marrow samples is followed, generally every 3 months for up to 3 years.

3.4 Other Patient Populations in Whom the Drug May Be Used

Arsenic trioxide has not been shown to have therapeutic benefit in diseases other than acute promyelocytic leukemia. Research on use of this agent for other disease indications has not progressed beyond basic science. Substantial preclinical and clinical research will be necessary before this drug can be considered for other indications.

While studies have not as yet been carried out in pediatric populations the underlying pathogenesis of APL is the same in children as it is in adults. It is therefore reasonable to use arsenic trioxide to treat children with APL and t(15; 17).

4 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

A patient advocacy group, the Leukemia & Lymphoma Society of Canada ("LLSC"), provided input on arsenic trioxide (Trisenox) for the treatment of acute promyelocytic leukemia ("APL"), which is summarized below.

LLSC conducted an online survey for patients who had survived APL and their caregivers in Canada. The survey was posted on the LLSC website and distributed through social media channels and e-mailed to known APL patients. The survey received a total of 9 responses (8 APL patients and 1 caregiver). In addition to the online survey, LLSC also held interviews with two additional patients asking the same questions that were noted in the survey. A total of 11 respondents (10 APL patients and 1 caregiver) were included in the submission.
Patients were diagnosed between 2006 and 2013. The average age of the survivors was 43. The LLSC recognizes this is a small sample, but considers that this is a rare disease with less than 100 people diagnosed a year and there was a great degree of similarity in the responses from the respondents, LLSC believes this information adds value to the pCODR process.

From a patient perspective, respondents would like to see an effective treatment for APL with fewer long-term side effects. LLSC reported that the majority of patient with APL who make it through their initial days of diagnosis and treatment are successfully cured of the disease. While some respondents treated with arsenic trioxide may experience some nausea, it was reported to be much milder than experiences with chemotherapy, and respondents felt that it could be controlled with supportive therapies. Respondents believe that it is highly important a patient is treated with the right medications to ensure remission.

Please see below for a summary of specific input received from the patient advocacy group.

4.1 Condition and Current Therapy Information

4.1.1 Experiences Patients have with APL

According to LLSC, acute promyelocytic leukemia ("APL") is a rare cancer. APL can develop as a primary cancer or can be related to treatment for a previous cancer. Based on the results of the survey, nine (9) respondents had primary APL; one had treatment related APL (previously treated for breast cancer).

LLSC states that most patients are diagnosed due to unwarranted nose bleeds, bruising and rashes, along with ongoing, debilitating fatigue. Patients are often feeling very ill when they are diagnosed. For some patients, diagnosis can be delayed depending on if they went to a hospital when first experiencing symptoms or waited to see a family physician or go to a walk-in clinic. Blood counts are generally abnormal.

Treatment is dependent on how quickly the results are read and the patient is transferred to a cancer centre that can appropriately treat the disease. This type of leukemia progresses rapidly and requires immediate hospitalization for treatment upon diagnosis, with the first phase of therapy usually lasting approximately 4 weeks. Treatment may last for 3 years. The length of treatment varied depending on whether the characterization of the APL was low-risk or high-risk.

According to the responses, five (5) respondents received consolidation treatment as in-patients and five (5) respondents received it as out-patients. Nine (9) respondents received

maintenance therapy as an out-patient. However, a patient with treatment related APL received maintenance therapy as an in-patient.

None of the respondents were able to work through their induction and consolidation therapy. A limited number were able to work at least part time through their maintenance therapy.

From a patient perspective, patients believe that they currently have no choice in the type of treatment. As this is an acute disease, delays can have huge impacts on the disease progression and the patient's health. Due to the rarity of APL, only a small number of cancer centers across the country treat this particular disease.

Respondents also noted that it is highly important a patient is treated with the right medications to ensure remission.

4.1.2 Patients' Experiences with Current Therapy for APL

According to the survey, APL patients were treated with a combination of all-trans retinoic acid and chemotherapy for their induction therapy. All of the respondents reported low blood counts (requiring transfusion of blood products), hair loss and extreme fatigue during treatment.

- Nine out of ten respondents reported nausea.
- Six (6) respondents reported intestinal issues.
- Two (2) respondents experienced Retinoic Acid Syndrome due to their treatment with all-trans retinoic acid.

Other side effects included rashes, mouth sores, temporary blindness (due to bleeding in the retina), sweats, bone pain, frequent infections and extreme headaches. The majority of these side effects were caused by the common chemotherapy drugs used to treat APL.

From a long-term perspective, seven (7) respondents have reported ongoing life-changing fatigue and memory issues due to chemotherapy; five (5) respondents reported infertility due to chemotherapy (one other patient is undergoing testing right now due to problems conceiving); and three (3) respondents reported issues with depression and anxiety requiring medical intervention. One (1) respondent has developed myelodysplastic syndrome (MDS) due to chemotherapy and is waiting for a stem cell transplant. One (1) other respondent experienced 'bone death' due to chemotherapy and is awaiting bilateral hip replacement.

Five (5) respondents also stated ongoing effects of treatment have affected their quality of life and indicated treatment side effects continue to affect how they are able to live day-to-day post treatment.
LLSC noted that high-risk patients receive more all-trans retinoic acid and more chemotherapy for their consolidation treatment. As in induction treatment, the immediate side effects of chemotherapy are harsh and the long-term effects can be debilitating. Patients who have low-risk disease may receive only all-trans retinoic acid for their consolidation therapy, which can be administered as an out-patient. However, this can often takes hours each day due to waiting for blood tests, waiting for the pharmacist to prepare the drug, waiting for a chair/bed in the clinic, etc. Five (5) of the respondents found that treatment as an out-patient still dominated the patient's life.

LLSC reported that all respondents were treated within their community except one, who was treated at a cancer centre outside the respondent's place of residence. Even those who live within the community still faced travel costs for treatment. Once they moved to out-patient care, traveling to the cancer centre for treatment each day for 40+ days is costly, especially if they are not well enough to drive themselves and do not have caregiver support. One patient reported "*Travel was the most difficult. Although I have a high income I cannot afford the cost of a volunteer driving me to treatment and the bus is not an option due to fatigue. I would have liked to have subsidized home care for the entire duration of my treatment.*" Five (5) respondents had expenses due to travelling for treatment and the same number reported costs for supportive care medications.

Since APL affects a younger demographic than other subtypes of AML, respondents noted that childcare was an issue, as was balancing family life while in hospital and while receiving treatment as an out-patient. Even though some respondents received a degree of homecare support when being treated as an out-patient, all said the support was not enough and they either had to pay for more help themselves or find family and friends to help them manage day-to-day during treatment.

Seven (7) respondents reported loss of income due to diagnosis and treatment of APL. Most of the respondents who indicated this as a problem were out of work for at least a year due to APL. Four (4) respondents reported they can no longer work to the same capacity they did prior to treatment, with two (2) reporting they needed to change careers as they could no longer meet the expectations of their previous jobs post-cancer. One (1) respondent said "*Tried my best to work in the profession I did before, but I had to change jobs to find something less demanding and less stressful*." One (1) respondent, who is still in treatment, has indicated that the respondent's position was in jeopardy during the respondent's illness and the employer may issue a dismissal for being unable to fill the role unless the respondent can commit to returning to work within 3 months.

LLSC stated that patients who were treated with all-trans retinoic acid and chemotherapy, and then relapsed, were treated with all-trans retinoic acid and arsenic trioxide. LLSC was not aware of any person who has relapsed after being treated with arsenic trioxide.

4.1.3 Impact of APL and Current Therapy on Caregivers

There was only one caregiver who responded to this survey. Two patients with children also responded on behalf of their spouse to certain questions regarding the effects of cancer on the caregiver.

LLSC reported that caregivers all experienced a degree of loss of work due to their loved one's diagnosis and treatment of APL. Since patients are in hospital for an extended period of time, they wish to be with them during treatment and also have added duties at home caring for children. Once patients moved to out-patient care, transportation back and forth to the hospital for treatment was often the caregiver's responsibility, as well as nursing them through the initial side effects of the treatment, while caring for children. One respondent said "*My husband's life became taking care of kids on top of working fulltime*." One respondent indicated her husband left during her treatment as it was too much for him to handle emotionally and has subsequently filed for divorce. One respondent also said "*It was a very difficult journey, which required a lot of help from others. Not sure what a person would do if they were alone or did not have a lot of support*."

The caregivers reported picking up extra responsibility coordinating home life and caring for the home, often continuing long past the end of treatment. In some cases, spouses have also had to adapt to the fact that biological children are no longer a possibility. Caregivers also reported depression and anxiety since their loved one's diagnosis. Two of the three respondents reported that support services available to help the family through the cancer experience were limited and did not meet their needs

4.2 Information about the Drug Being Reviewed

4.2.1 Patient Expectations for and Experiences To Date with Arsenic trioxide

LLSC indicated that patients who relapse or do not respond to the all-trans retinoic acid/chemotherapy regimen in Canada are treated with arsenic trioxide through a special access program. Since the drug was previously not approved in Canada, it was purchased internationally when needed. The respondents commented on how a drug could be considered the standard of care for relapsed patients by oncologists in Canada, yet the drug is not available in Canada. Respondents believe the cost of procuring the drug this way when needed would be expensive, and there were worries about the delay in procurement.

LLSC reported that the majority of patients with APL who make it through their initial days of diagnosis and treatment are successfully cured of the disease. LLSC noted that patients are not necessarily willing to tolerate a new medication that has limited results in the short-term only; however, LLSC believes that this would not be the case with this drug since arsenic trioxide works when traditional therapy does not appear to, with lasting remissions and with fewer toxic side effects.

Respondents would prefer to receive a drug as part of their treatment that has better long-term remission data. All respondents would like to see an effective treatment with fewer long-term side effects (basically less or no chemotherapy since the chemotherapy drugs cause the majority of these long-term effects) and think this is highly important moving forward.

Like the other treatments, arsenic trioxide is administered intravenously in a hospital setting so this is not a change for patients.

One respondent received arsenic trioxide when they did not respond to initial traditional therapy. It was reported that the respondent responded to the treatment and went into remission. The individual did not experience side effects from the arsenic trioxide; however, they did have long-term issues from the chemotherapy treatment that they received initially. Generally, patients need to be closely monitored for heart irregularities as arsenic in high dosages can cause issues. The respondent to this survey did not have any problems in this area.

While some respondents treated with arsenic trioxide experienced some nausea, it was reported to be much milder than experiences with chemotherapy, and respondents felt that it could be controlled with supportive therapies.

4.3 Additional Information

None were provided.

5 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

The following issues were identified by the Provincial Advisory Group as factors that could affect the feasibility of implementing a funding recommendation for Arsenic trioxide (Trisenox) for acute promyelocytic leukemia (APL). The Provincial Advisory Group includes representatives from provincial cancer agencies and provincial and territorial Ministries of Health participating in pCODR. The complete list of PAG members is available on the pCODR website (www.pcodr.ca).

Overall Summary

Input on Arsenic trioxide (Trisenox) for APL was obtained from eight of the nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. From the PAG perspective, the main enabler is the unmet need for the relapsed/refractory APL patients. Barriers to implementation include the daily one-hour intravenous infusions and monitoring for serious events listed in the black box warning. The daily administrations require additional chair time or hospital admission and presents resource challenges for smaller clinics and hospitals. Monitoring and treating serious adverse events also requires additional resources.

Please see below for more details.

5.1 Factors Related to Comparators

In the first line setting, ATRA in combination with anthracycline with or without cytarabine is the current treatment used. As this regimen is inexpensive, the relative cost of arsenic trioxide would present as a barrier to its use in the first-line setting.

PAG noted that there is no current standard treatment of APL in the relapsed/refractory setting where there is an unmet need for this patient population and where most of the trials are in this setting.

5.2 Factors Related to Patient Population

The number of patients in the relapsed/refractory setting would be small and arsenic trioxide could potentially fill the gap in therapy for this patient population, which would be enablers. The number of patients would be higher in the first-line setting, which could be a potential barrier.

PAG also noted the potential for indication creep, particularly for treatment of myelodysplastic syndrome, which would be a barrier.

5.3 Factors Related to Accessibility

The daily intravenous administration requires hospital admission in locations where outpatient infusion centres are unavailable on a 7 days/week basis. This presents a barrier to access on weekends when many outpatient centres are not open. It is also difficult for patients to travel an outpatient clinic on a daily basis and for patients in rural areas where outpatient clinics are not available.

5.4 Factors Related to Dosing

PAG noted that during the induction phase, arsenic trioxide is administered daily as an inpatient and in the consolidation or maintenance phase, arsenic trioxide is administered daily for five or six days per week in the outpatient clinics. PAG questioned whether the 25 doses over a five week period is evidence-based, as this modified administration regimen would be an enabler as it could be delivered Monday to Friday rather than 25 consecutive days.

It was also noted that the dosing of arsenic trioxide is mg/kg which may lead to potential dosing errors as most chemotherapy is mg/m^2.

5.5 Factors Related to Implementation Costs

PAG has noted barriers to implementation are the additional chair time for intravenous infusions and drug wastage due to only one vial size being available. Although this would be a small number of patients, the daily one-hour infusions for up to 60 doses require additional health care resources to administer. Additional resources are also required to monitor for serious adverse events, electrocardiograph changes and electrolytes.

As some jurisdictions have used arsenic trioxide through Health Canada's Special Access Program, there is some familiarity with its administration and this is an enabler. However, PAG noted that administration may be limited to the cancer clinics with the expertise to administer arsenic trioxide or be limited to inpatient setting for those patients who require electrocardiographic monitoring during infusion, which would be barriers.

5.6 Other Factors

The black box warning for APL differentiation syndrome and QT prolongation would present as barrier as more resources are required to monitor and manage patients for these serious adverse events.

PAG is requesting pERC address the issues with treatment algorithm with respect to first-line treatment, relapsed/refractory setting and retreatment. PAG is also requesting that pERC comment on the use of ATO in pediatric patients in both the first line and relapsed refractory settings.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the effectiveness of Arsenic Trioxide (ATO) as a single agent, or in combination with ATRA and/or other chemotherapy agents, on patient outcomes compared with appropriate comparators in treatment of patients and associated subgroups with:

i. Previously untreated Acute Promyelocytic Leukemia

ii. Relapsed/Refractory Acute Promyelocytic Leukemia

No Supplemental Questions relevant to the pCODR review or to the Provincial Advisory Group were identified.

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the Clinical Guidance Panel and the pCODR Methods Team. Studies were chosen for inclusion in the review based on the criteria in the table below. Outcomes considered most relevant to patients, based on input from patient advocacy groups are those in bold.

Table 1. Selection Criteria

Previously Untreated - First Line Setting				
Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Randomized controlled trials	Previously untreated diagnosed APL, Subgroups – elderly, frail	Trans-Retinoic Acid: (ATRA) AND Trisenox (Arsenic Trioxide: ATO)	ATRA + Anthracycline Chemotherapy OR ATRA + Anthracycline Chemotherapy + other Chemo agents	**OS, DFS,PFS, EFS, QOL, Hematological and Non-Hematological toxicities:** neutropenia, hypokalemia thrombocytopenia, hyperglycemia, coagulopathy, hyperleukocytosis, severe hemorrhage, bleeding disorders, Abnormal EEG/QT intervals,differentiation Syndrome, Neuropathy

Relapsed/refractory Setting				
Randomized controlled trials In the absence of RCT data, fully published non-randomized clinical trials investigating the efficacy of ATO were to be included. Exclude reports of trials with only a dose-escalation design. Reports of trials with a mixed design[†] were to be included only if separate data were reported for the cohort of patients who received the study intervention.	Relapsed or refractory diagnosed APL, Subgroups – elderly, frail	Trans-Retinoic Acid: (ATRA) AND/OR Trisenox (Arsenic Trioxide: ATO)	ATRA + Chemotherapy OR ATRA + Chemotherapy + Allogenic Stem Cell Transplant OR ATRA + Chemotherapy + Autologous Stem Cell Transplant	**CR,OS, EFS,DFS,PFS, QoL, Hematological and Non-Hematological** toxicities: neutropenia, hypokalemia thrombocytopenia, hyperglycemia, coagulopathy, hyperleukocytosis, severe hemorrhage, bleeding disorders, Abnormal EEG/QT intervals, differentiation Syndrome, Neuropathy
Abbreviations: ATO=Arsenic Trioxide; ATRA=all trans-retinoic acid; ASCT=autologous stem cell transplantation; CR=complete response; iv=intravenously; OS=overall survival; PFS=progression-free survival; PR=partial response; QOL=quality of life; RCT=randomized controlled trial * Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions) [#]If study design was non-randomised, a comparator was not necessary. In the absence of a trial that randomised ATO vs an appropriate comparator, a study with ATO in both arms was acceptable.				

6.2.2 Literature Search Methods

The literature search was performed by the pCODR Methods Team using the search strategy provided in Appendix A.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-2013) with in-process records & daily updates via Ovid; EMBASE (1980-2013) via Ovid; The Cochrane Central Register of Controlled Trials (2013, Issue 2) via Wiley; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Arsenic Trioxide (Trisenox), and Acute Promyelocytic Leukemia. Methodological filters were applied to limit retrieval to randomized controlled trials for the first line setting review. This filter was not applied for the relapse/refractory review. Retrieval was limited to the human population using an appropriate filter. Retrieval was not limited by publication year. Retrieval was limited to the English language. The search is considered up to date as of January 27, 2014.
Grey literature (literature that is not commercially published) was identified by searching the websites of regulatory agencies (Food and Drug Administration and European Medicines Agency), clinical trial registries (U.S. National Institutes of Health – clinicatrials.gov and Ontario Institute for Cancer Research – Ontario Cancer Trials) and relevant conference abstracts. Searches of conference abstracts of the American Society of Clinical Oncology and

the American Society of Hematology (ASH) were conducted but not limited by date. Searches were supplemented by reviewing the bibliographies of key papers and through contacts with the Clinical Guidance Panel. In addition, the manufacturer of the drug was contacted for information as required by the pCODR Review Team.

6.2.3 Study Selection

One member of the pCODR Methods Team selected studies for inclusion in the review according to the predetermined protocol. All articles considered potentially relevant were acquired from library sources. Two members of the pCODR Methods Team independently made the final selection of studies to be included in the review and differences were resolved through discussion.
Included and excluded studies (with reasons for exclusion) are identified in section 6.3.1.

6.2.4 Quality Assessment

Assessment of study bias was performed by one member of the pCODR Methods Team with input provided by the Clinical Guidance Panel and other members of the pCODR Review Team. SIGN-50 Checklists were applied as a minimum standard. Additional limitations and sources of bias were identified by the pCODR Review Team.

6.2.5 Data Analysis

No additional data analyses were conducted as part of the pCODR review.

6.2.6 Writing of the Review Report

This report was written by the Methods Team, the Clinical Guidance Panel and the pCODR Secretariat:

- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental questions.
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions on the net overall clinical benefit of the drug.
- The pCODR Secretariat wrote summaries of the input provided by patient advocacy groups and by the Provincial Advisory Group (PAG).

6.3 Results

6.3.1 Literature Search Results

First Line Setting: A total of 142 unique citations were identified through searches of MEDLINE (OVID), MEDLINE Daily Update (OVID), MEDLINE In-Process & Other Non-Indexed Citations (OVID), EMBASE (OVID), Cochrane Central Register of Controlled Trials, and PubMed (Figure 1). Thirty eight additional abstracts were identified through searches of the annual conferences of ASCO and ASH. Of those 180 citations, 29 potentially relevant reports were retrieved for full text review. Three reports were included in the pCODR systematic review and twenty six reports were excluded. Studies were excluded because they were meta-analysis and did not follow randomized trial procedures or were non-comparative trials (cohort)[25-27], had invalid comparators per inclusion criteria[28-36], were interim reports of trials included[37, 38], was a non-randomized trial[39], were not published in English[40, 41], or treated relapsed patients[42]. Eight duplicates were also removed. A clinical summary as well as statistical reviews on Trisenox, completed by the United States Food and Drug Administration's (U.S. FDA) was also included in the submission by the manufacturer to pCODR.

Relapse Refractory:
A total of 1832 unique citations were identified through searches of MEDLINE (OVID), MEDLINE Daily Update (OVID), MEDLINE In-Process & Other Non-Indexed Citations (OVID), EMBASE (OVID), Cochrane Central Register of Controlled Trials, and PubMed (Figure 2). Of those 1832 citations, 20 potentially relevant reports were retrieved for full text review. Thirteen reports were included in the pCODR systematic review and seven reports were excluded. Studies were excluded because they were meta-analysis[43], had fewer than 10 patients enrolled in the study[44], contained comparison of first line therapy only[45], or were study types that did not meet inclusion criteria.[46-49] Only fully published studies were included while abstract only studies were not retrieved. Two studies were excluded because they were only reported as abstracts[5,9].

Figure 1. QUOROM Flow Diagram for Inclusion and Exclusion of studies (First line)

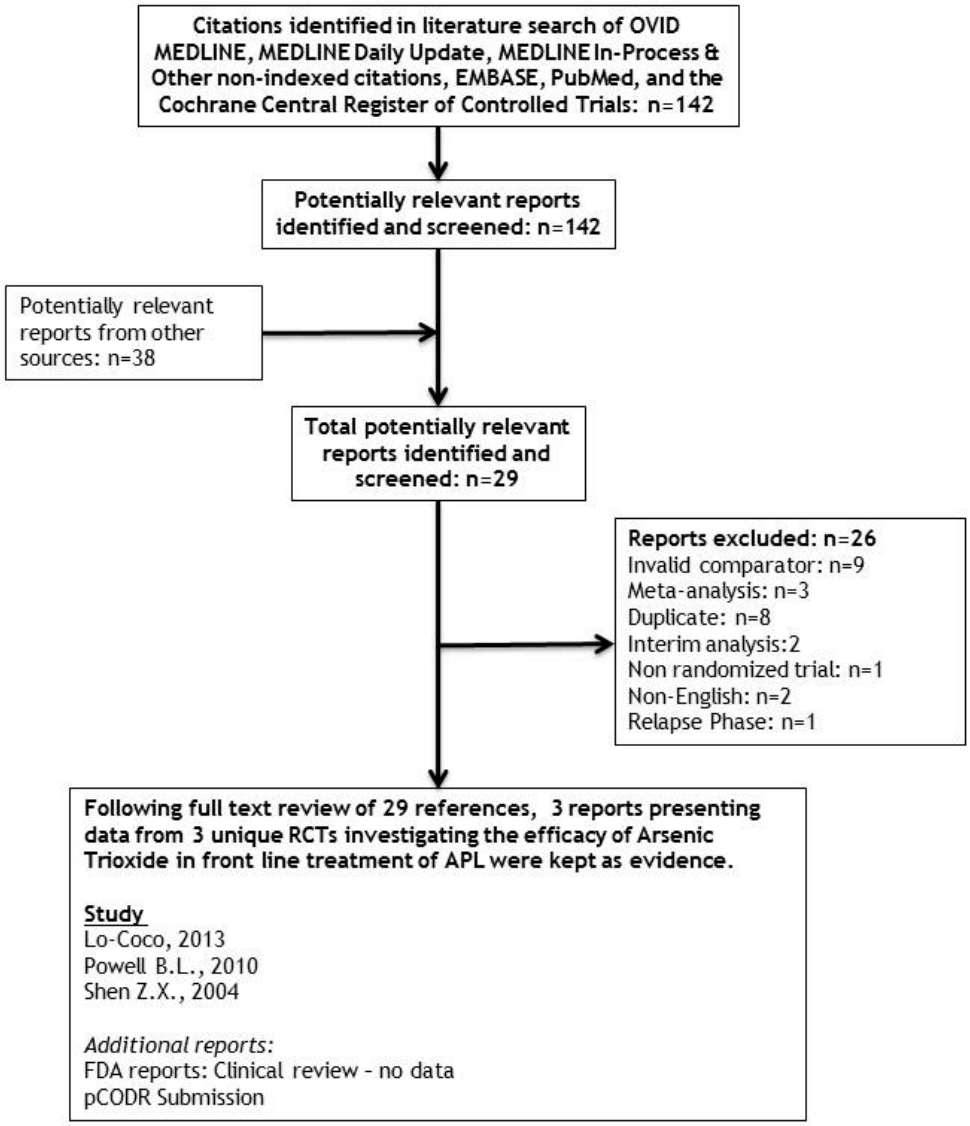
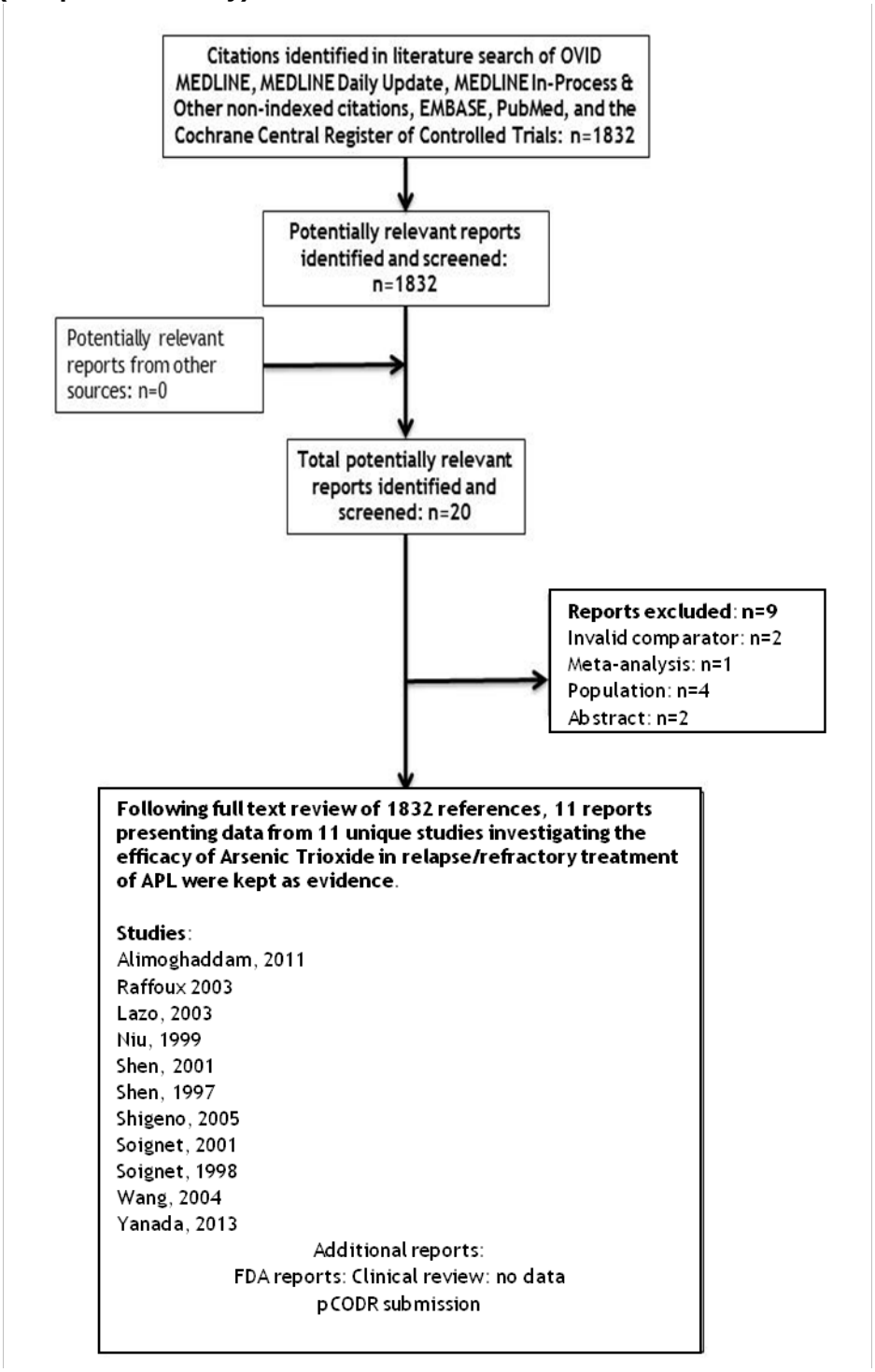


Figure 2. QUOROM Flow Diagram for Inclusion and Exclusion of studies (Relapse/Refractory)



6.3.2 Summary of Included Studies

6.3.2.1 Detailed Trial Characteristics

Table 2. Summary of "frontline setting" Trial characteristics of the included Study[1,2,3]

Trial Design	Key Inclusion Criteria	Intervention and Comparator	Outcomes
ATO in Induction & Consolidation			
Lo-Coco 2013 Phase III, Multicenter Industry sponsored Italy & Germany Oct, 2007-Sept, 2010 **Trial Type:** comparative, Non-inferiority with no cross over. Blinding/randomization process completed centrally, but procedures not reported. **Sample Size:** 156, 77 – ATRA/ATO, 79 – ATRA/Chemo	• Eligible patients were 18 to 71 years of age with newly diagnosed APL classified as low-to-intermediate risk (white-cell count at diagnosis, ≤10×10^9 per liter). • World Health Organization (WHO) performance status score of 2 or lower • Creatinine level of 3.0 mg per deciliter or lower (≤265 µmol per liter) • Bilirubin level of 3.0 mg per deciliter or lower (≤51 µmol per liter) **Exclusion criteria:** High Risk Cases. Defined as those with initial WBC count of greater than $10X10^9$ per litre.	ATRA (45 mg/m^2/day for 15 days) plus arsenic trioxide (ATO - 0.15 mg/kg/day – 5 days/week)for induction and consolidation therapy vs ATRA (45 mg/m^2/day for 15 days) + idarubicin (12 mg/m2/day on days 2, 4, 6, 8 induction; 5 mg/m^2/day on days 1-4 consolidation) mitoxantrone (10 mg/m2/day on days 1-5 2nd consolidation) methotrexate (15 mg/m^2/week) oral 6-mercaptopurine (6-MP) (50 mg/m^2/day) alternating with ATRA for 15 days every 3 months for two years	Primary: 2 yr EFS Secondary: Rate of complete remission, 2 yr DFS, prob. 2 yr OS, cumulative incidence relapse, minimal residual disease, NCO toxicity
ATO in Induction Phase			
Shen 2004, Phase III – 3 arm **Academic funding**	**Inclusion criteria:** newly diagnosed APL **Exclusion criteria:** prior exposure to any anti-	ATRA (n=20, 25 mg/m^2 per day until CR was achieved) *vs*	Median DFS, rate of CR **Not stated whether these were primary or secondary endpoints.

China April 2001-Feb, 2003 **Trial Type:** comparative, no cross over, Blinding/randomization not reported. **Sample Size:** 61, 20 – ATRA, 20 - ATO 79, 21 – ATRA/ATO	leukemic therapy	ATO (n=20,0.16 mg/kg per day until CR) *vs* ATRA (25 mg/m^2 per day until CR was achieved) plus ATO (0.16 mg/kg per day until CR) (n=21)	
ATO in Early Consolidation Phase			
Powell 2010, Phase III Randomized Controlled Trial Academic and industry funding **Location:** 5 North American Cooperative groups **Apr, 2001- Feb, 2003** **Trial Type:** comparative, no cross over, Blinding/randomization not reported. **Analysis pop:** Previously untreated APL **Sample Size:** 481, 237 – ATRA, 244 – ATRA/ATO	**Inclusion criteria:** Clinical diagnosis of APL with subsequent confirmation of PML-RAR by RT-PCR assay	Standard induction ATRA (45 mg/m^2/day, twice-daily on day 1 until CR or day 90) + cytarabine (200 mg/m^2 daily as a continuous iv infusion on days 3 – 9), + daunorubicin (50 mg/m^2 iv daily on days 3 - 6) Early consolidation therapy Two 25-day courses of ATO (0.15 mg/kg daily iv over 1 hour for 5 days per week for 5 weeks) given after the standard induction and before standard consolidation standard consolidation 2 courses of ATRA (45 mg/m^2 daily for 7 days) + daunorubicin (50 mg/m^2 iv daily on the first 3 days) **vs.** Standard induction (as above)	Primary: 3 yr EFS Secondary: 3 yr DFS, OS, NCI Toxicity, Response rates, Relapse rates

		No early consolidation Standard consolidation (as above)	

Table 2. Summary of "relapsed/refractory setting" Trial characteristics of the included Study			
ATO Relapse/induction			
Trial Design	Key Inclusion Criteria	Intervention and Comparator	Outcomes
Alimoghaddam 2011, Single arm - Prospective Cohort Academic funding **Iran** **May, 1999-Jan, 2010** **Sample Size:** 31	**Inclusion criteria:** Relapsed APL following treatment with ATRA/Chemo. Diagnosis of these relapsed cases was suggested by their clinical presentation, histomorphology of their peripheral blood and bone marrow, aspiration/biopsy, and proven by detection of PML-RARa by RT-PCR.	Use of ATO as salvage therapy ATO (0.15 mg/kg iv infusion until CR or a maximum of 60 days)	CR rate, 2year OS, 2year DFS Patients were also evaluated for intravascular coagulation, electrolyte imbalance, liver and renal function, EEG abnormalities, and APL differentiation.
Lazo 2003, Single arm Propsective Cohort Industry funding Jul, 1998-May, 2001 Sample Size: 12	**Inclusion criteria:** Confirmation of t(15;17) by conventional cytogenetic analysis or positive reverse transcriptase-polymerase chain reaction (RT-PCR) assay for PML-RAR or fluorescence in situ hybridization (FISH) showing evidence of RAR_ or PML translocation; adequate renal function (creatinine≤ 2.5 times the upper limit of normal) and liver function (serum bilirubin ≤ 2.5 times the upper limit of normal); negative pregnancy test; and signed informed consent.	• Use of ATO as induction relapse therapy • ATO (0.15 mg/kg per day iv until CR or a maximum of 60 days)	CR, molecular remission, toxicity

Table 2. Summary of "relapsed/refractory setting" Trial characteristics of the included Study			
ATO Relapse/induction			
	All patients did receive subsequent therapy following treatment with ATO that included ATO alone, ATO and other chemotherapeutic agents, and idarubicin plus ATRA without ATO.		
Niu 2007, Single arm prospective trial **Jun, 1997-May, 2009** **Sample Size:** 47	**Inclusion criteria:** Diagnosis of APL established on the basis of clinical presentation, morphological criteria of the French-American-British (FAB) classification, cytogenetic evaluation for t(15;17), and reverse transcription polymerase chain reaction (RT-PCR) analysis for PML-RARa transcripts.	Use of ATO as induction relapse therapy ATO (10 mg iv over 2 to 3 hours per day, for 6-weeks).	CR, toxicity, DFS
Raffoux 2003, Randomized Control Trial Institutional funding**1998-2001** **Sample Size:** 20	**Inclusion criteria:** APL in first or subsequent relapse were eligible for the study if they were aged 12 years or more and not presenting visceral contraindication to arsenic therapy. All patients previously treated with ATRA-containing chemotherapy	Use of ATO versus ATO and ATRA as induction relapse therapy ATO (0.15 mg/kg/day over a 3hour iv infusion) + ATRA (45 mg/m^2/d orally starting on day 1 of ATO administration until CR)	Time to CR, safety, molecular response
Shen 2001, Prospective cohort compared with historic control (prospective cohort) academic funding **Sample Size:** 20	**Inclusion criteria:** Diagnosis established according to the FAB criteria, good performance status (ECOG 3), and no prior arsenic treatment. Patients had chromosomal translocation t(15;17) and/or PML-RARa expression and one patient was t(15;17) and PMLRARa-negative. No	Use of ATO as induction relapse therapy Prospective cohort treated with: • ATO (0.08 mg/kg iv over 2 h per day, for successive 28 Days) Historical control cohort treated	CR, toxicity Patients were also evaluated for toxic events – hepatic, APL differentiation, 2 year OS, and 2 year DFS.

Table 2. Summary of "relapsed/refractory setting" Trial characteristics of the included Study			
ATO Relapse/induction			
	complex karyotype was observed in this group	with: • ATO (0.16 mg/kg daily, with each course lasting almost 6 weeks.)	
Shen 1997, Single arm prospective Cohort with no comparison academic funding **Sample Size:** 15	**Inclusion criteria:** The diagnosis was based on clinical data (history, symptoms, and physical findings), examination of peripheral blood and bone marrow (BM) according to FAB classification, the karyotype, and RT-PCR analysis for PML-RARa transcripts.	Use of ATO as induction relapse therapy • ATO (10 mg/d iv over 2 – 3 hrs until CR achieved)	CR, Adverse events
Shigeno 2005, Non-randomized single arm Prospective cohort Industry funding Mar. 1999-Aug. 2004 **Sample Size:** 34	**Inclusion Criteria:** relapsed and refractory APL	Use of ATO as induction relapse therapy • ATO (0.15 mg/kg administered until bone marrow remission to a maximum of 60 days)	CR, 2year OS, 2year EFS, toxicity Patients were also evaluated for cardiac toxicities, APL differentiation, liver dysfunction, and neuropathy.
Soignet 2001, Non-randomized, single arm, Prospective trial Industry funding **Sample Size:** 40	**Inclusion Criteria:** Diagnosis of either relapsed and/or refractory APL by bone marrow morphology. Confirmation was obtained in blood or bone marrow mononuclear cells by conventional cytogenetics showing t(15;17), by positive RT-PCR assay for PML/ RAR-∞, or by fluorescence in situ hybridization (FISH) analysis that showed evidence of RAR--∞ or PML translocations.	Use of ATO as induction relapse therapy • ATO (0.15 mg/kg daily to a maximum of 60 doses or until all leukemic cells in bone marrow were eliminated)	CR, toxicity, 18 month OS and RFS Patients were also evaluated for cardiac toxicities, APL differentiation and leukocytosis.

Table 2. Summary of "relapsed/refractory setting" Trial characteristics of the included Study			
ATO Relapse/induction			
	Written consent also required. Forty patients experiencing first (n = 21) or second (n = 19) relapse. Exclusion Criteria: Patients were excluded if they were receiving concurrent treatment with cytotoxic chemotherapy, radiation or investigational agents, if they had a history of grand mal seizures, if they had active serious infections that were not controlled by antibiotics, or if serum creatinine or bilirubin was ≥ 2.5 mg/dL.		
Soignet 1998, Single arm, non-randomized prospective trial Industry funding **Sample Size:** 12	**Inclusion Criteria:** diagnosis of APL confirmed by cytogenetic analysis or fluorescence in situ hybridization for patients with a t(15;17) translocation, or by the reverse-transcription polymerase-chain-reaction (RT-PCR) assay for PML–RARalpha fusion transcripts. In addition, patients had to have relapsed after standard therapy that included all trans retinoic acid plus a combination of cytotoxic drugs. Written consent was required.	Use of ATO as induction relapse therapy • Initially ATO was fixed at between 10-15 mg/day, but was changed to weight adjusted regimen of 0.15 mg per kilogram of body weight per day until visible leukemic cells were eliminated from the bone marrow.) • Median dose range was from 0.06 to 0.2 mg/kg per day	CR, adverse events, gene expression
Wang 2004, Two arm, non-randomized, prospective cohort (ATO & ATO/ATRA) compared	**Inclusion Criteria:** Diagnosis of APL Based on clinical manifestations, morphological criteria according to the French–	Use of ATO as induction relapse therapy • ATO-alone group: 10 mg ATO iv	CR rate, toxic side effects Patients were also evaluated for mortality

Table 2. Summary of "relapsed/refractory setting" Trial characteristics of the included Study			
ATO Relapse/induction			
with historical cohort (ATRA alone) **Sample Size:** 28 in relapse	American–British classification, and reverse transcription polymerase chain reaction (RT-PCR) analysis for PML/RAR_transcripts (80 newly diagnosed patients, 28 relapsed patients)	over 3–4 h/day • ATO/LD-ATRA group: ATO (10 mg/day iv) + ATRA (10 mg 3 times per day, half the conventional dose) • Historical cohort (ATRA alone)	
Yanada 2013, Non-randomized, phase 2, clinical trial Academic funding **Sample Size:** 35	**Inclusion Criteria:** Documentation of cytogenetic and/or molecular evidence of t(15;17)/PML-RARa was required at the time of entry. (35 patients (26 with hematologic and 9 with molecular relapse) age between 18 and 65 years; an ECOG performance status between 0 and 3; and adequate functioning of the liver (serum bilirubin level 2.0 mg/L), kidneys (serum creatinine level, 2.0 mg/dL), lungs (PaO2>60 mm Hg or SpO2>93%), and heart (no severe abnormalities detected on electrocardiograms). Written informed consent required. **Exclusion Criteria:** Patients having previously undergone autologous or allogenic SCT not eligible.	Use of ATO as induction and consolidation therapy • sequential treatment consisting of induction (0.15 mg/kg until CR or a maximum of 60 days) and consolidation (0.15 mg/kg for 25 days) with ATO, peripheral blood stem cell (PBSC) harvest after high-dose cytarabine chemotherapy, and autologous hematopoietic cell transplantation (HCT)	CR, 5 year EFS,OS
ATRA=All Trans Retinoic Acid**; ATO=**Arsenic Trioxide**; NCO=**Cardiotoxicity**; SCT=**Stem cell transplant**; CR**= complete response; **DB**= double-blind; **PC**= placebo controlled; **PR**= partial response; **RECIST**= Response Evaluation Criteria in Solid Tumours; **RCT**= randomized controlled trial			

a) Trials

First Line Setting

Three randomized trials were found for this review. One trial evaluated the use of ATO in both induction and consolidation treatment. Another trial evaluated the use of ATO in induction treatment only. The final trial evaluated the use of ATO in early consolidation treatment. The trial evaluating the use of ATO in both induction and consolidation was a non-inferiority trial, while the other two were superiority trials. There was limited information presented regarding the methods used for blinding and randomization from all trials.

Trials investigating the addition of Arsenic Trioxide to Induction & Consolidation

The Lo-Coco 2013[1] study investigated the use of Arsenic Trioxide in induction and consolidation phases. This was an open label, phase III, non-inferiority trial designed to test whether ATRA-ATO was not inferior to ATRA-chemo with respect to 2 year event free survival rates. Non-inferiority was assessed by estimating the two sided 95% confidence interval for the between group difference in crude 2 year EFS rates and then checking that against the lower bound of the 95% confidence interval. Enrollment and randomization was based solely upon morphologic features, and genetic information required for inclusion was carried out by reference laboratories. 162 patients were enrolled and 156 were analysed. Patients were randomized to receive ATRA plus arsenic trioxide for induction and consolidation or standard ATRA-idarubicin induction followed by three cycles of consolidation with ATRA plus chemotherapy and maintenance with low dose chemotherapy. Randomization was done centrally. Survival analysis was completed by comparing Kaplan-Meier curves, and between groups comparison was completed with use of the Log-rank test. Event free survival was defined as at 2 years after diagnosis, with treatment failure defined as any of the following: no achievement of hematologic complete remission after induction therapy, no achievement of molecular complete remission after three consolidation courses, molecular relapse, hematologic relapse, or death. Disease-free survival was defined as time from achievement of hematologic complete remission to relapse (either molecular or hematologic), persistence of PCR positivity after consolidation therapy, or death, whichever occurred first. Overall survival and cumulative incidence of relapse were defined according to the NCI workshop definitions. Kinetics of minimal residual disease was defined as the kinetics of PML-RARA transcript reduction after induction and consolidation therapy. The study met the reported sample size requirement.

Trials investigating the addition of Arsenic Trioxide to Induction

The Shen, 2004[3] study examined the use of arsenic trioxide in induction therapy and was an open label, three arm, clinical trial. Patients were required to have confirmed diagnosis that was confirmed with cytogenetic assay, and no exposure to anti-leukemic therapy. Patients were randomized to arsenic trioxide, ATRA, or a combination of both. Analysis of bone marrow aspirates at three different points was used to determine outcomes which included complete remission and disease free survival. Complete response (CR) was defined as the absence of clinical evidence, HB>100 g/liter, neutrophils > 1.5 X10^9/liter, platelets >100 X 10^9/liter, and BM morphology that reveals normmocullularity with <5% promyelocytes and absence of auer-rod containing leukemic cells. Differences between continuous variables were analysed using Wolcoxin rank-sum test, whereas the Chi-squared test, including fischer's Exact test was used for categorical variables. Kaplan-Meier curves were compared in survival analysis.

Consolidation therapy included one of each: DA regimen (daunorubicin, 45 mg/m^2 per day for 3 days; Ara-C, 100 mg/m^2 per day for 7 days), Ara-C ''pulse'' regimen (Ara-C, 1.5–2.5 g/m^2 per day for 3 days), and HA regimen (homoharringtonine, 2–3 mg/m^2 per day for 3 days; Ara-C, 100 mg/m^2 per day for 7 days).

Maintenance treatments were different for each of the three groups: **group 1** (ATRA, 25 mg/m^2 per day for 30 days; then 6-mercaptopurine,100 mg/day for 30 days or 15 mg of methotrexate once a week for 4 weeks), **group 2** (ATO, 0.16mg/kg per day for 30 days; then 6-mercaptopurine, 100 mg/day for 30 days or 15 mg of methotrexate once a week for 4 weeks), and **group 3** (ATRA 25mg/m^2 per day for 30 days; then ATO 0.16 mg/kg per day for 30days; then 6-mercaptopurine, 100 mg/day for 30 days or 15 mg of methotrexate once a week for 4 weeks). The above regimens for maintenance treatments were applied for five cycles. No definitions for disease free survival were found in the article.

Trials investigating the addition of Arsenic Trioxide to Early Consolidation

The Powell, 2010[2] study investigated the use of arsenic trioxide in initial consolidation following induction, for untreated APL. The study was a 2-arm, double randomization design conducted by 5 North American cooperative groups (CALGB, Eastern Cooperative Oncology Group, Southwest Oncology Group, Children's Oncology Group, and National Cancer Institute of Canada Clinical Trials Group). Cases were randomized at registration to maintenance treatment. If patients achieved hematologic remission, they continued directly to consolidation which depended on initial randomization. The primary endpoint for this trial was event free survival (EFS) and disease free survival (DFS). Eligibility for Powell, 2010[2] required diagnosis of APL and subsequent confirmation of PML-RARα by RT-PCR assay at one of 3 cooperative group laboratories. Consolidation therapy began within two – four weeks of achieving hematologic remission. Survival comparisons were completed using log-rank tests, and Kaplan-Meier survival curves were used to estimate 3yr EFS and 3yr DFS. Event free survival was defined as the time from study entry to first event. An event was defined as failure to achieve a CR, relapse after achieving a CR, or death. Disease-free survival (DFS) was defined as the time from attainment of a CR to relapse or death. Overall survival was defined as the time from study entry to death.

Relapse Refractory Setting

See trial characteristics described in Table 2.

b) Populations

First Line Setting

There were 156 cases from Lo-Coco, 2013[1], 481 from Powell, 2010[2], and 61 from Shen, 2004[3] for a total 698 patients. Analyses were carried out based upon the intention to treat principle. Per protocol was also included in Lo-Coco, 2013[1] for the primary endpoint (EFS).

All three trials included patient characteristics tables, and all included patient gender, age, white blood cell count, and platelet count. In Lo-Coco, 2013[1] the median age was 44.6 years with a range of 19.1 – 70.2 years for the ATRA/ATO arm and 46.6 yrs with a range of 18.7 – 70.2 years for the ATRA/Chemo arm. In Powell, 2010[2] 83% patients were between the ages of 15 yr – 60 yr in the non-ATO arm, and 85% of patients were in the same group for the ATO arm. Lastly in Shen, 2004[3] median age was 30.5yrs, 39.5yrs, and 34yr for the ATRA, ATO, and ATRA+ATO arms respectively. The top end of the age range for each category was 74, 69, and

62 indicating that the age distribution between arms could be causing bias in favor of ATO given that age is a risk factor. It also creates further uncertainty regarding the randomization and allocation procedures that were used in this trial.

Patient gender was evenly matched across each trial. Lo-Coco, 2013[1] reported 52% male and 48% female, on the ATRA/ATO arm and 46% and 54% male and female on the ATRA/Chemo arm. Powell, 2010[2] reported 52% male and 48% female on the non-ATO arm and 50% male and female on the ATO arm. Shen, 2004[3] reported 60%/40% male/female for the ATRA arm, 45%/55% male/female for the ATO arm, and 57%/43% male/female for the ATRA/ATO arm. Patient race was reported in Powell, 2010[2] but not in Lo-Coco, 2013[1] or Shen, 2004[3]. Due to the fact that Shen, 2004[3] was conducted in China it is assumed that all patients were of the Chinese race. Powell, 2010[2] reported 83%/80% white, 6%/8% African American, 4%/3% Hispanic, and 7%/9% Other for non-ATO/ATO arms respectively.

Risk levels were reported in Lo-Coco, 2013[1] and in Powell, 2010[2]. Risk levels, defined by white blood cell count, were defined differently in each trial and were not consistent across trials in that the Lo-Coco[1] trial excluded high risk cases. For these two trials risk levels were comparable between treatment arms. The proportion of low risk patients from Lo-Coco, 2013[1] was 43% and 34%, and 57% and 66% high risk, for the ATRA/ATO and ATRA/Chemo arms respectively. Powell, 2010[2] had 28% and 28% low risk, 47% and 49% intermediate risk, and 25% and 23% high risk patients for ATRA/ATO and ATRA/Chemo arms respectively. Risk categories were not assigned in Shen, 2004[3].

White blood cell counts were included in patient characteristics and also helped define patient risk groups. In Lo-Coco, 2013[1] median WBC counts were comparable with $1.49x10^9$/L and $1.60x10^9$/L for ATRA/ATO and ATRA/Chemo arms respectively. Powell, 2010[2] had median WBC counts of $2.2x10^9$/L and $2.4x10^9$/L in ATO and Non ATO arms respectively, and Shen, 2004[3] had median WBC counts of $3.0x10^9$/L, $2.7x10^9$/L, and $2.1x10^9$/L for ATRA, ATO, and ATRA/ATO arms respectively.

Platelet counts were also reported in patient characteristics tables for all three trials. Lo-Coco, 2013[1] reported median platelet counts of $31x10^9$/L and $27x10^9$/L for ATRA/ATO and ATRA/Chemo arms respectively. Powell, 2010[2] reported median platelet counts of $29.5x10^9$/L and $30x10^9$/L for Non ATO and ATO arms respectively, and Shen, 2004[3] reported $23x10^9$/L, $27x10^9$/L, and $30x10^9$/L for ATRA, ATO, and ATRA/ATO arms respectively.

b) Populations

Relapse Refractory Setting

Alimoghaddam, 2011[6] reported that the median age of patients was 27 yrs with a range from 10yrs-79yrs. The study also reported median white blood cell and platelet count at relapse as being 5.8×10^9/L (0.5×10^9 –44×10^9) and 34×10^9/L (2×10^9 – 261×10^9).

Lazo, 2003[7] reported that 25% of patients were under age of 60, 42% with Leukocyte count ≥ $3X10^9$, 58% with Granulocyte count ≤10^9/L and Platelet count ≤$50X10^9$/L. The study also reported that 8% of cases had creatinine ≥ 1.5 mg/dl and 17% of cases had a total bilirubin ≥ 1 mg/dl. There were a total of 12 patients in trial.

Niu, 2007[8] reported male/female proportion of 62%/38%, median age 38 (range: 7-55), median WBC 3.4 $X10^9$/L (range: 0.6 – 56.0), median RBC) 3.65 $X10^9$/L (range: 1.78 – 5.31), median hemoglobin 109 g/L (range: 56-180), median platelet 38 $X10^9$/L (range: 4-236) and median % blasts and promyelocytes in BM 66 (range: 12.5 – 95.0).

Raffoux, 2003[5] reported no significant differences between the randomization groups in terms of median age (P = .21), sex ratio, first versus subsequent relapse distribution, median WBC (P = .38), median platelet count (P = .82), median fibrinogen level (P = .89), and karyotype and molecular features.

Shen, 2001[9] reported the following patient characteristics: Age (range) - 6-55years, white blood cell count (Range) – (1.1 - 83.6 $X10^9$/L), Platelet count (range) – (12 - 186 $X10^9$/L), and hemoglobin range - 56-180 g/L.

Shen, 1997[10] reported the following patient characteristics at diagnosis: male/female distribution(67%/33%), age (range: 14yrs to 53yrs, white blood cell count (range: 0.6 - 67.5 $X10^9$/L), platelet count (range: 4 - 76 X 10^{12}/L), and APL cell % in bone marrow (range: 12.5 - 96.0 g/L).

Shigeno, 2005[11] identified patient characteristics for 34 patients included in the study. Median age was 47, gender ratio (male/female) was 22/12, number of relapses (1/2/>2) 11/17/6), prior SCT (yes/no) 5/29, and relapse type (BM/Molecular) 32/2. All patients had been previously treated with ATRA.

Soignet, 2001[12] reported gender proportion (male/female) of 40%/60%, age distribution of 12.5% <18 years, 67.5% 18 years-59yrs, and 20% ≥ 60 years. The study also reported the following: weight – 32.5% <75kg, 45% 75kg-100kg, 22.5% >100kg, and number of prior regimens with 47.5% having 1, 42.5% having 2, and 10% having >2. 87.5% of patients had prior BMT, and 47.5% had more than one relapse.

Soignet, 1998[13] reported individual characteristics for 12 patients. Age range was 9– 75 years, treatment duration range was 5 - 39 days, time to remission range was 24 – 83 days, time to platelet count of ≥100,000/mm^3 was 16 - 77 days (range) and time to leukocyte count of ≥3000/mm^3 was 16 - 83 days (range).

Wang, 2004[4] reported white blood cell count, hemoglobin, and platelet count, for the three comparator groups. Otherwise there was limited information regarding patient demographics. In the ATO/low dose ATRA treatment group, the overall male/female distribution was 1.56 and the median age as being 35 years (range: 13 to 62 years). In this group the percentage of APL cells was 0.8 (range: 0.33 to 0.95). White blood cell count was 4.9X109/L (range: 0.8 to 14.0). Hemoglobin was 59 g/L (range: 33 to 150), and platelet cell count was $39X10^9$/l (range: 5 to 75). In the retrospective cohort treated with ATRA alone, patients had a percentage of APL cells of 0.66 and a range of 0.29 to 0.94. White blood cell count was $4.4X10^9$/L and a range of 1.0 to 11.2. Hemoglobin was 63 g/L with a range of 42-134, and platelet cell count was $40X10^9$/L and a range of 8.4 to 84. In the prospective cohort treated with ATO alone group, the ratio of females to males was 1.89 and the median age was 34 years (range: 12 to 63 years). This group also had percentage of APL cells of 0.79 ranging from 0.31 to 0.90. White blood cell counts were $5.2X10^9$/L (range: 1.2 to 10.3). Hemoglobin was 68 g/L (range: 47-148), and platelet cell counts were $37X10^9$/L (range: 6 to 78).

Yanada, 2013 reported median age of 46 (range: 20-64), male/female count of 23/12, WBC count median of $2.6X10^9$/L (range: 0.5 – 18.1), median platelet count $79x10^9$/L (range: 8-260), performance status 0/1/2/3 of 27/6/0/2, number of prior relapses 1 (n=32) and 2 (n=3), type of relapse hematological/molecular of 26/9, and median interval between diagnosis and enrollment in years of 2.5 (range: 0.8-11.0).

c) Interventions

First Line Setting

Trials investigating the use of arsenic trioxide in the first line treatment of acute promyelocytic leukemia used slightly different therapies in terms of treatment stage. ATO dosages were the same between the Lo-Coco, 2013[1]study and the Powell, 2010[2] study, with consolidation treatment lasting a maximum of 4 months in Lo-Coco,2013[1] and and 3 months in Powell, 2010[2]. There was a 0.01 mg/kg/day difference is dose between these and the Shen, 2004[3] trial, although the phase of treatment was different. In Shen, 2004[3] ATO was given during induction until CR was achieved.

Arsenic Trioxide interventions were administered in different phases of treatment in each of the trials. Lo-Coco, 2013[1] administered ATO as part of both induction and consolidation, Powell, 2010[2] administered ATO as part of early consolidation prior to chemotherapy, and Shen, 2004[3] used ATO during induction phase only.

Relapse Refractory Setting

Interventions in the relapsed/refractory setting were quite variable. Some regimens involved use of ATO exclusively, some ATRA and ATO, some ATO and chemotherapy agents, and some with ATO and chemotherapy and stem cell transplant (autologous/allogeneic). Alimoghaddam, 2011[6] evaluated the use of ATO as a single agent in the treatment of relapsed APL. For this prospective cohort arsenic trioxide was administered as a 0.15-mg/kg/day two hour iv infusion until complete remission (CR) or a maximum of 60 days. Upon achieving CR, patients received consolidation treatment six days a week for 28 days. Patients received 2 course of consolidation therapy with one month between treatments. Patients were also given two additional courses of consolidation therapy.

Lazo, 2003[7] used a treatment regime that included daily intravenous dose of 0.15mg/kg until patients achieved a CR or for a maximum of 60 days. Patients who achieved CR could receive up to four maintenance cycles starting 4 weeks after completion of induction therapy. Dosing for maintenance treatment was the same as that used in induction treatment. Subsequent maintenance courses were repeated after intervals of 4 weeks off therapy.

Niu, 1999[8] administered 10 mg ATO as an intravenous drip over 2 to 3 hours per day, for 6-weeks duration. If necessary, a second course was performed after an interval of 7 days. Those patients who failed to reach CR after 2 courses were considered as non-responders and were treated with chemotherapy. Follow-up therapy for consolidation included three different protocols. Protocol 1 included continuous chemotherapy with daunorubicin ($45mg/m^2/d$ on day 1 to 3) or mitoxantrone (8 mg/d on day 1 to 3), and Ara-C (100 to 200 mg/d on day 1 to 7) with one course every 2 months in the first year, every 3 months in the second year and every 4 months in the third year. Protocol 2 included 10 mg ATO daily for 28 to 30 days as a course with approximately 30 to 60 days interval between two cycles within the first year, followed by a 7 to 14 days course every 2 months over the second and third year. Protocol 3 was a chemo and ATO combination. Administration was the same as listed above for each group, and ATO was administered along with chemotherapy.

Raffoux, 2003[5] contained two cohorts receiving either ATO alone or in combination with ATRA. ATO was administered at a dose of 0.15 mg/kg/d as a 3-hour intravenous infusion. ATO was administered for a maximum of 56 days, until CR achievement, severe toxicity (grade 2 to 4, depending on the organ concerned), or the arsenic serum concentration's reaching 10^{-5} M or greater. To prevent potential arsenic-related neurotoxicity, all patients received vitamin B1 (250 mg/d) and clobazam (10 to 30 mg/d) during treatment. The regimen followed in the

ATRA arm involved ATRA administered at a dose of 45 mg/m^2/d orally starting on day 1 of ATO administration until CR achievement. No post remission therapy protocol was specified, and no second ATO cycle was planned for patients who were resistant. Patients were generally offered HSCT (allogenic or autologous) and consolidation cycles of ATO were considered as information began to indicate appropriateness of this therapy. Consolidation included administration of ATO at 0.15 mg/kg/d, for 28 consecutive days, either with or without ATRA according to initial randomization.

Shen, 2001[9] had a low dose and conventional dose ATO groups. The low dose group regimen was ATO (0.08 mg/kg as an intravenous drip over 2 h per day, for successive 28 days). If necessary, a second course was carried out after an interval of 14 days. The conventional group received a daily dose of 0.16 mg/kg and each course lasted for almost 6 weeks. Patients that failed to reach CR after two courses were considered as non-responders and were treated with chemotherapy. All patients were treated with consolidation therapy following achievement of CR. This included DA chemotherapy with dose and courses that varied by patient.

Shen, 1997[10] used a treatment protocol that included 10 mg ATO added to 500 ml 5% glucose-normal saline for IV drip on 2 to 3 hours once a day. A 0.1% solution was prepared for use as IV drip over 2-3 hours a day, until CR. After CR, the treatment was discontinued for 30 days. Then a second course of ATO was used for 28 days as consolidation therapy.

Shigeno, 2005[11] used a treatment protocol that was ATO administered at a dosage of 0.15 mg/kg on a daily basis until bone marrow remission, up to a maximum of 60 days, as induction therapy. For consolidation, patients who achieved CR received an additional ATO course 3-6 weeks following CR. The same dosage was used in consolidation as was in induction. Consolidation was given for a cumulative total of 25 days. ATO maintenance therapy was provided to four patients who chose that option over intensive chemotherapy. Maintenance regimen was the same as consolidation and included 2 or more additional courses.

Soignet, 2001[12] used a treatment regimen that included induction ATO administered at a dose of 0.15 mg/kg given daily until bone marrow remission was observed. The prescribed daily dose was administered intravenously for 2 hours. Treatment was discontinued before 60 doses if the patient met the criteria for bone marrow remission or if substantial toxicity occurred. Patients who met eligibility criteria for CR were eligible for consolidation therapy beginning 3 to 4 weeks following completion of induction therapy. The dose for consolidation was the same as for induction. Consolidation was required to be completed within 5 weeks. Maintenance therapy was an option for patients who remained in CR following consolidation. Up to 4 additional cycles were possible at a dose schedule similar to consolidation. Eleven patients also underwent autologous transplant after ATO.

Soignet, 1998[13] followed a treatment regime for one cohort where initially patients received either 10 or 15 mg of arsenic trioxide per day as a fixed dose, but the referral of two children to the study prompted conversion to a weight-adjusted regimen that was 0.15 mg per kilogram of body weight per day. Median dose was 0.16 mg per kilogram (range, 0.06 to 0.20). This was continued until visible leukemic cells were eliminated from the bone marrow. Bone marrow mononuclear cells were serially monitored by flow cytometry for immunophenotype, fluorescence in situ hybridization, RT-PCR assay for PML-RAR-alpha fusion transcripts, and Western blot analysis for expression of caspases 1, 2, and 3. Treatments were infused intravenously over a period of two to four hours once per day. Patients who had complete remission were eligible for treatment with additional courses of therapy three to six weeks after the preceding course. Subsequent courses were generally given at a dose of 0.15 mg per kilogram per day for a cumulative total of 25 days; the drug was administered either daily or

on a weekdays-only schedule, for a maximal total of six courses over a period of approximately 10 months.

Yanada, 2013[14] followed a treatment regime where induction included ATO (0.15 mg/kg) administered as a 2hr infusion until CR or a maximum of 60 days. In addition, patients received 12 mg/m^2 of idarubicin (IDA) on days 1 and 2 if 1 or more of the following criteria were met when the treatment was started: (1) the white blood cell (WBC) count exceeded 20.0 x 10^9/L; (2) the combined total count of myeloblasts and promyelocytes in the peripheral blood exceeded 5.0 x10^9/L; and (3) there was the presence of an extramedullary myeloid tumor. Patients with cytological evidence of CNS leukemia received intrathecal injections twice a week simultaneously with ATO, until complete clearance of leukemic cells in the cerebrospinal fluid (CSF) was achieved. Those who achieved CR were scheduled to receive an additional 2 courses of ATO (0.15 mg/kg for 25 days) for consolidation. If therapy went to a third course of ATO, patients proceeded to PBSC harvest. In this case high-dose Ara-Cwas administered at 2 g/m^2 for 3 hours twice daily for 4 days, and granulocyte–colony-stimulating factor was initiated from day 6. Upon recovery, autologous PBSCs were harvested by means of apheresis. Patients who attained a target CD34+ cell dose of 2.0 x 10^6/kg or higher were allocated to undergo autologous HCT unless PML-RARalpha transcripts were detected in PBSCs. Conditioning consisted of busulfan (1 mg/kg orally every 6 hours on days 26 to 24) and melphalan (70 mg/m^2 intravenously on days 23 to 22), whereas unpurged autologous PBSCs were infused on day 0.

Wang, 2004[4] examined the use of ATO as a single agent as well as in combination with ATRA for remission induction, and consolidation, treatment phase of relapse. Some patients in the ATO/ATRA and prospective ATO alone groups had previously failed ATO containing regimens in the first line setting. ATO-alone group received 10 mg ATO as an intravenous infusion over 3–4 h/day. For the ATO/LD-ATRA group, ATO was administered intravenously at a dose of 10 mg/day and ATRA was given orally three times per day at a dose of 10 mg (half the conventional dose). No details were provided on the use of ATRA in the historical cohort group. Patients in the three groups who had achieved CR were given consolidation therapy which included chemotherapy for one or two cycles followed by ATO consolidation-therapy. Chemotherapy consisted of cytosine arabinoside (Ara-c, 100 mg/m2) given by intravenous infusion every 12 h for seven consecutive days, and daunorubicin (45 mg/m2) administered daily by intravenous infusion for the first 3 days. ATO consolidation-therapy consisted of a 3-year programme: a 28-day treatment with 10 mg/day ATO given at 1-month intervals for the first year, 2-month intervals for second year and 3-month intervals for the third year.

c) Patient Disposition

First Line Setting

None of the included trials reported that they included all randomized patients in the final intent to treat analysis. Lo-Coco, 2013[1] enrolled 162 cases, 156 were included in the intention to treat analysis. Powell, 2010[2] enrolled 518 patients and 481 were randomized and reported in the intention to treat analysis. Shen, 2004[3] enrolled 61 patients and all were analysed.

Relapse Refractory Setting

Due to the fact that all but one study were not randomized trials a discussion of randomization procedures, and methods for planned sample analysis, were not described. Raffoux, 2003[5] was a randomized trial but did not indicate the methods used for randomization or concealment. However, comparisons between the randomized groups were

not used as part of this evidence review because they reflect results of comparison that is not valid to our research objective.

d) Limitations/Sources of Bias

First Line Setting

- Non-inferiority trial design used in Lo-Coco, 2013[1] requires consideration of the limitations imposed by this study type. In non-inferiority trials the aim is to show that a new product is not unacceptably worse than an older one. Assay sensitivity is the main concern and is defined as the ability of a trial to distinguish and effective therapy from one that is not effective. For example, a superiority trial without assay sensitivity may not show efficacy while a non-inferiority test based upon the same trial would show non-inferiority. It has been shown that non-inferiority trials tend to reward trial procedures that are methodologically poor-quality and that it is easier to show non-inferiority.[50, 51]
- Regarding non-inferiority trial design there is also issue with how to determine the non-inferiority margin which is at discretion of investigators. A standard does not exist in these trials, although the 95% confidence interval is often used. Because there is only a comparison with the lower bound of the confidence interval it is possible for an outcome in which non-inferiority is achieved while the test drug is actually inferior. This happens when the entire distribution of results lies between the lower bound CI, and 0. Although sensitivity testing was also completed in an attempt to claim superiority in the main outcome, EFS, there remains the possibility that use of non-inferiority analyses can bias in favor of Arsenic Trioxide and does not ensure that efficacy is superior. Ie. Might be not superior it is reported to be statistically "non-inferior". In a non-inferiority trial there is no protection against a blinded investigator biasing the results toward a preconceived belief in equivalence by assigning similar ratings to the treatment responses of all patients. Given that this was an open label trial there is increased likelihood that bias was introduced into results.
- Of the three trials used in the review none had adequate descriptions of randomization procedures, blinding, or concealment. Randomization procedure, blinding methods, and concealment methods were not detailed within the sources we found for all trials included. This has the potential to create bias in favor of ATO. Without an understanding of these methods this bias needs to be accounted for in interpretation of results.
- Lo-Coco, 2013[1] and Powell, 2010[2], used event free survival as the primary outcome and were both adequately powered to detect significant differences in EFS, DFS, and overall survival. Shen, 2004[3] used DFS as an endpoint but it could not be determined from the publication whether the trial was adequately powered to detect a difference. When DFS was reviewed in Shen, 2004[3] there was no test for superiority and a median DFS was reported for each arm. There was however no description of how DFS was calculated in Shen, 2004[3]. There was no description of intended follow-up period, results were presented in months not as a probability, and no comparative analysis was undertaken. Furthermore Kaplan-meier survival curves presented in the article have different follow up periods for each group and DFS does not appear to correspond with months indicated in follow up based on the horizontal axis. Due to this unclear reporting there is considerable uncertainty as to the reliability of the results presented in the Shen 2004 study.
- CR was defined differently between trials and as a result the comparability of results between trials is compromised. In Lo-Coco, 2013[1] hematologic complete remission and hematologic relapse were defined according to the National Cancer Institute workshop definitions. In Powell, 2010[2] they are defined by the 1990 NCI criteria, and in Shen, 2004[3] it was defined explcitley as "Achievement of CR demanded that Clinical evidence of APL

be absent, untransfused Hb be >100 g/litre, neutrophils be >1.5 X 10^9/litre, platelets be >100 X$10^{9/}$litre, and BM morphology reveal normocellularity, with <5% promyelocytes and absence of Auer rod-containing leukemic cells". Based on the definition of CR in each trial, the same patients may not be considered eligible for consolidation. Timing of CR is also problematic in that assessment of response may create bias when timing used creates higher/lower response rates.

- Age and age range shown in the ATO/ATRA arm from Shen, 2004[3] indicate that age distribution may be causing bias. Because of the fact that patient age is positively correlated with inferior outcomes in patients with APL it could be that better outcomes are reported in the ATO/ATRA arm because of age group characteristics within.
- The population tested in the Shen, 2004[3] was made up of Chinese ethnicity exclusively. As a result the generalizability of these results to other ethnicities may be limited and need to be interpreted with caution. The population in Powell, 2010[2] also had limitations in that the inclusion criteria was quite broad, disease severity was not homogenous, and different centers involved may have a variety of non-standardized treatment processes. Although many centres were also involved in Lo-Coco, 2013[1] there were very detailed inclusion criteria and protocol definitions.
- Maintenance treatment in Shen, 2004[3] was also variable between groups, but matched the initial induction therapy. Because of this it is difficult to separate the benefit of adding ATO during induction or consolidation phase which leaves a question regarding timing of ATO therapy.
- No quality of life data was reported in any of the trials used in this review. It is expected if chemotherapy was replaced by Arsenic Trioxide there would be less adverse events (hematologic), and higher quality of life. However, reported adverse events with ATO are severe. There was no ability to compare quality of life and further analysis of quality of life is needed.
- Reporting of toxicities in Powell, 2010[2] was limited and did not provide reasonable evidence as to which treatment produced better toxicity outcomes.
- Further follow-up of cases would improve the validity of results as cases are only followed up with short periods for all three studies. Median follow up period in Lo-Coco[1] was 34.4 months, 18 months in Shen, 2004[3], and median follow-up of 54 months in Powell, 2010[2]. Results have short follow up period and with continued follow up changes in efficacy and long-term toxicities are possible.

Relapse Refractory Setting

- Major sources of bias limit ability to confirm relapse/refractory study results with certainty. These are small trial sample sizes, variability in population characteristics, and challenges comparing non-homogenous cohorts because of how complete remission is measured and treatment protocols differ.
- In general, single arm clinical trials have limitations with respect to the conclusions that can be drawn from them. As the trials included had only a single arm or no eligible comparator, they provide no comparative evidence regarding the efficacy of arsenic trioxide in relation to any other treatment. There was one RCT included as part of the systematic review (Raffoux 2003) however it had ATO in both arms and as such did not present an appropriate comparator arm. One included study, Wang 2004, was a non-randomised single arm trial that had a historical cohort comparator arm of patients that received ATRA alone. Recognizing the limitation with the historical comparison (not a prospective randomised comparison) and the sample size (n=36), this study provided some comparative data versus ATRA.

- Trial sample sizes were all very small and follow up periods quite short. Sample size ranged from 12 (Soignet, 1998[13]) – 47 (Niu, 1999[8]). Given that APL is an uncommon disease it becomes more difficult to acquire large samples. These small studies do make validity and generalizability difficult because they are not representative and do not lack the power to make valid confirmatory conclusions. Further, the lack of comparative studies makes interpretation of these results more difficult because there is no way to review consistency of superiority between trials.
- Alimoghaddam, 2011[6] was conducted in Iran and contained patients of only Iranian race. Niu, 1999[8], Shen 2001, Shen 2004, and Wang, 2004[4] were conducted in China, and study populations were restricted to patients of Chinese ethnicity. Shigeno, 2005[11] and Yanada, 2013[14] were limited to patients of ethnicity. The limitation of generalizability also applies to the results of these studies because they are ethnicity specific. However, as the studies were carried out in centres across many nations and similar efficacy results have been found, the results may be generalizable across a large range of ethnicities.
- Each trial discusses the achievement of complete remission (CR) as an endpoint. Some studies indicate how CR is measured while others do not. CR is measured at different points in treatment between studies as well. These between study differences in measurement of CR achievement do have an impact, albeit not measured, that could significantly modify the results included in this evidence base.
- Finally, there are significant between study differences in treatment protocols including variability in the number of consolidation cycles. Heterogeneity in treatment protocols makes pooling of results from the relapse/refractory setting inappropriate as comparisons are invalid and ability to generalize results is impossible. In this review it is necessary to account for the difference in protocol in making a conclusion regarding the use of arsenic trioxide and the protocol within which it is used. Protocols for trials have been described in detail in section 6.3.2, subsection e.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Efficacy Outcomes - First Line Setting					
Author, Year (ref)	**Comparison**	**MFU (median follow up)**	**EFS**	**DFS**	**OS**
Arsenic Trioxide in induction and consolidation					
Lo-Coco, 2013[1]	ATRA + ATO	34.4 ms	***2 yr*** 97% (p<0.001)	***2 yr*** 97% (95% CI, 94-100), p=0.11	***2 Yr*** 99% (95% CI, 96-100), p=0.02
	ATRA + Chemo		86%	90% (95% CI, 84-97)	91% (95% CI, 85-97)
Arsenic Trioxide to Early Consolidation					
Powell, 2010[2]	ATRA & Chemo	na	***3 yr*** 63% (p<0.0001)	***3 yr*** 70% (p<0.0001)	***3 yr*** 81% (p<0.07)
	ATRA & Chemo + ATO		80%	90%	86%
Arsenic Trioxide to Induction					
Shen, 2004[3]	ATRA	18 ms	na	13 ms	na
	ATO		na	16 ms	na
	ATRA + ATO		na	20 ms	na
Efficacy Outcomes - Relapsed/Refractory Setting					
Author, Year (ref)	**Intervention**	**MFU (median follow up**	**EFS**	**DFS**	**OS**
Alimoghaddam, 2011[6]	ATO	32 mths	na	54.6%	81.1%
Lazo, 2003[7]	ATO	24 mths	na	na	na
Niu, 1999[8]	ATO	na	na	1yr/2yr 63.6%/ 41.6%	na
Raffoux 2003[5]	ATO vs. ATRA/ATO	na	na	na	na

Shen, 2001[9]	Low dose ATO vs. standard dose ATO	na	na	RFS at 12 months and 24 months was 78.57% and 49.11%	OS The estimated OS at 12 months and 24 months were 92.86% and 61.55%
Shen, 1997[10]	ATO	na	na	na	na
Shigeno,2005[11]	ATO (initial and one consolidatio	30 mths	17%	na	56%
Soignet, 2001[12]	ATO induction, conslдtion, maintnce, transplant	na	18 mth RFS 56%	na	18 mnth 66%
Soignet, 1998[13]	ATO	na	na	na	na
Wang, 2004[4]	ATO with low-dose ATRA (LD-ATRA) – 3 regime comparison	na	na	na	na
Yanada, 2013[14]	Induction and Consolidation ATO	4.9 yrs	5 yr 65%	na	5 yr 77%

Event Free Survival (EFS)

First Line Setting

Two of the three trials used EFS as the primary endpoint. Lo-Coco, 2013[1] reported 2 yr EFS and had a median follow up of 34.4 months. Results indicated that the addition of ATO to the induction and consolidation treatment produced outcome that was at least not inferior to, and possibly superior to, the current standard of ATRA/Chemo (p<0.001).
Powell, 2010[2] analysed 3 yr EFS and also conducted subgroup analysis on high risk, low/intermediate risk patients. Results indicated that the addition of ATO during early consolidation treatment created superior 3 year event free survival rates of 80% versus 63% (p<0.001). Results of subgroup analyses also showed significant difference in EFS in favor of ATO arm. Low intermediate risk, p=0.0003, and high risk, p=0.015. Median follow up was 54 months. Upon request by pCODR follow up EFS data was provided by the manufacturer for the Lo-Coco, 2013[1] study but was deemed to be non-disclosable by the manufacturer. The information was assessed by pCODR and was deemed to have no major impact on the review and as such, the follow-up data was not included in the systematic review.

Relapse/Refractory Setting

Shigeno, 2005[11] and Yanada, 2013[14] each reported EFS rates. Shigeno, 2005[11] reported estimated 2 yr EFS of 17%, while Yanada, 2013[14] reported 5 yr EFS of 65%. It should be noted that treatment protocol in Yanada, 2013[14] included stem cell transplant, following induction and consolidation with ATO. The treatment protocol in Shigeno, 2005[11] included induction and one phase of consolidation if CR not achieved.

Disease Free Survival (DFS)

First Line Setting

All three trials reported DFS, but only two tested for superiority between groups. Lo-Coco, 2013[1] reported 2 yr DFS rates of 97% and 90% for ATRA/ATO and ATRA/Chemo respectively. Results of testing showed no significant difference between the two treatment arms when ATO is used in both induction and consolidation versus ATRA/Chemo (p=0.11). Powell, 2010[2] reported a significant difference between the two treatment arms, 90% ATO and 70% non-ATO, in early consolidation (p<0.0001). In subgroup analysis of low/intermediate and high risk groups a significant difference in DFS was found in both risk groups, between treatment arms (p<0.0001). It was also found for DFS that there was no significant difference between high risk and low/intermediate risk patient groups in the ATO consolidation arm indicating no difference in efficacy of regime between low risk and high risk cases. Disease free survival was not tested between treatment arms in Shen, 2004[3]. Median DFS was reported for each group.

Relapse/Refractory Setting

Disease free survival was reported in two studies: Alimoghaddam, 2011[6]and Niu, 1999[8]. Alimoghaddam, 2011[6] reported 2 year DFS of 54.6%. Niu, 1999[8] reported 1 year and 2 year DFS rates of 63.6% and 46.6%.

Overall Survival (OS)

First Line Setting

Overall Survival was reported in two of the three trials. Lo-Coco, 2013[1] reported 2 yr overall survival probability of 99% and 91% in the ATRA/ATO arm and ATRA/Chemo arms respectively. This was a statistically significant difference, p=0.02, with ATRA/Chemo being non-inferior. Powell, 2010[2] reported 3 yr overall survival that was 86% and 81% in the ATO and non-ATO

arms respectively but the results were not significant (p=0.07) for alpha equal to 0.05. When subgroup analysis was applied there were no differences in OS in terms of treatment arm, although the ATO arm always showed some improvement.

Relapse/Refractory Setting

Overall survival was reported in five of the eleven studies included in the systematic review for the relapse/refractory setting. Alimoghaddam, 2011[6] reported 1year and 2 year OS of 86.9% and 81.1%. Shen, 2001[9] reported 2 year OS of 61.55%, Shigeno, 2005[11] reported 2 year OS of 56%, Soignet, 2001[12] reported 18 months OS of rate of 66%, and Yanada, 2013[14] reported 5 yr OS of 77%.

Overall survival results were also quite variable between studies.

Complete Remission (CR)

First Line Setting

CR was not defined as an endpoint for review in first line setting outcomes.

Relapse/Refractory Setting

A review of complete remission rates shows a range of 71% (Wang, 2004[4]) to 100% (Lazo, 2003[7]). The median complete remission rate across studies was 85%. The Wang study which included some patients that had received ATO in the first line setting reported that there was no significant difference in outcomes for patients that had previously failed ATO containing treatment regimens in the first line setting.

Quality of life (QoL)

Quality of Life is not well reported in the included studies for both first line, and second line, therapy with ATO. Although efficacy in terms of EFS was significant, OS was not found to be statistically different, in Powell, 2010[2]. In Lo-Coco, 2013[1] arsenic trioxide was found to be non-inferior to chemotherapy, in combination with ATRA, in induction and consolidation. Because these results indicate the efficacy of arsenic trioxide is similar to that of chemotherapy in terms of survival, it is critical to incorporate more quality of life data to assess other potential outcomes important to patients. Quality of life results are not well reported for both first line and the relapsed/refractory indications. This represents a large gap in information required to determine overall efficacy of arsenic trioxide in the treatment of APL.

Harms Outcomes

Deaths

First Line Setting

Patient deaths were reported in Lo-Coco, 2013[1]. In detail, four patients in the ATRA-chemotherapy group died during induction therapy, 2 from the differentiation syndrome, 1 from ischemic stroke, and 1 from bronchopneumonia. Finally, four patients died during consolidation therapy, 3 in the ATRA/chemo arm and one in the ATRA/ATO arm. Three patients in the ATRA-chemotherapy group died from hemorrhagic shock, pulmonary embolism, and bronchopneumonia. The patient from the ATRA/ATO group died from bronchopneumonia associated with the H1N1 virus.

Powell, 2010[2] reported nineteen patients from each arm died in induction therapy and no treatment related deaths during consolidation phase. When reported as subgroup analysis by risk group, low, medium and high risk, the proportions of deaths were 4%, 4%, and 20%. No description of cause was provided.

Shen, 2004[3] reported four deaths during induction therapy. Notably, all died of intracerebral hemorrhage. There was no further follow up or discussion of these cases and their complications.

Relapse/Refractory Setting

Four patient deaths reported in Alimoghaddam, 2011[6] occurred during the induction phase and were the result of APL differentiation syndrome (1), intracranial hemorrhage (2) and disease progression (1). One patient death was reported in Lazo, 2003[7] resulting from sepsis, and four deaths Niu, 1999[8] as a result of cerebral hemorrhage. Nui, 1999 also reported two deaths following ATO treatment but no cause was given. Septic shock with seizures and ATO induced differentiation syndrome with hyperleukocytosis were specified as causes for two patient deaths in Raffoux, 2003[5]. Six patient deaths were reported in Shen, 2001[9]. Two patients from the low dose group and three from the conventional dose group died of intracranial hemorrhage in the early phase of treatment. One in the conventional dose group died as a result of central infiltration of leukemia cells. Shen, 1997 reported two deaths following remission and no deaths during the treatment phase. Shigeno, 2005[11] reported one early death during induction resulting from cerebral hemorrhagic infarction, 5 deaths related to stem cell transplant following remission, 5 deaths due to relapse during chemo/ATRA postremission therapy, 1 death due to relapse during ATO postremission, 1 death due to relapse and one due to "other causes" in patients not undergoing any postremission therapy. The high number of deaths in Shigeno relative to other studies is likely because those deaths related to SCT are not usually reported in other studies. Soignet, 1998[13] reported one death on day one of therapy due to intracranial hemorrhage. Soignet, 2001[12] reported two deaths following the final study treatment. Direct relationship was not given for these deaths but intravascular coagulopathy and hemorrhage were given as contributing factors. Disseminated intravascular coagulation was the cause of all deaths occurring between days 8 to 18 following treatment, in the ATO and ATO/ATRA groups, in Wang, 2004[4]. Yanada, 2013[14] reported one patient death as result of intracranial hemorrhage immediately following enrollment and prior to ATO treatment.

Hematologic Toxicity

First Line Setting

All three trials reported the frequency of treatment related hematologic toxicity events. Lo-Coco, 2013[1] recorded grade 3 or 4 neutropenia and thrombocytopenia lasting greater than 15 days more frequently in induction and consolidation treatment phases, in the ATRA-chemotherapy group compared with the ATRA/ATO group. Twenty six episodes were reported in the ATRA-ATO group and 59 episodes in the ATRA/Chemo group representing a statistically significant difference given *alpha*=0.05 (p<0.001).
Powell, 2010[2] reported maximum hematologic adverse events due to consolidation treatments were 16% grade 3 and 67% grade 4 on the standard arm, and 21% grade 3 and 54% grade 4 on the As2O3-containing arm.

Shen, 2004[3] reported peripheral blood cell counts revealed earlier recovery of normal platelets counts (>100 X 10^{9}/liter) in group 3 (median, 22 days) over group 1 (median, 32 days, P=0.03) as well as group 2 (median, 33 days, P= 0.031) . Recovery time for both hemoglobin and white

blood cell counts were similar between the three groups. Hyperleukocytosis appeared earlier in the combined therapy group, but the frequency of occurrence and the between group differences in level did not reach statistical significance.

Relapse/Refractory Setting

Niu, 1999[8] reported hyperleukocytosis in 55% of patients while Shen, 2001[9] reported hyperleukocytosis in 40% of the low dose group patients. Soignet, 1998[13] reported six patients who developed leukocytosis.

Shigeno, 2005[11] reported 11 cases of hyperleukocytosis, and 8 of these were regarded as having developed APL differentiation syndrome. Severe neutropenia, anemia, and thrombocytiopenia was observed in 33 (97%), 23 (68%), and 21 (62%) patients respectively. Infectious events were seen in 11 (32%) patients and included febrile neutropenia, sepsis, or pneumonia. Varicella-zoster infections were observed in 8 (24%) patients.

Soignet, 2001[12] reported hypolakemia in 50% of patients, and neutropenia in 8% of 19 severe patient episodes. Evidence of clinical coagulopathy was found in 48% of cases and 35% of subclinical cases. 58% of these clinical and subclinical cases had adverse events related to coagulopathy. For all 40 patients at presentation 50% developed leukocytosis.

Incidence of Major Bleeding Events

First Line Setting

Shen, 2004[3] reported four cases that did not achieve CR and died as a result of major bleeding event. The event was intracerebral hemorrhage on day 2, 1, 15, and 8. None of the other trials included a discussion of major bleed events.

Severe hemorrhage and bleeding are adverse events that are quite important for patients with APL because of the higher risk of low platelet counts. The frequency of these events was not well described in the first line setting and this information was deemed important in order to fully understand impact of interventions on these events.

Information on severe (grade 3-4) hemorrhages was requested and obtained from the submitter. It was reported that there were only few severe hemorrhage events that occurred during this trial. [redacted] occurred in the ATRA arm, while [redacted] occurred in the ATO arm. [redacted] left frontal epidural hematoma one month following induction and [redacted] episode of hemorrhagic shock at induction therapy occurred in the ATRA arm. [redacted] cerebral hemorrhage, 6 days following induction occurred in the ATO arm.[52] *(Non-Disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the manufacturer that it can be publicly disclosed.)*

Relapsed/Refractory Setting

Intracranial hemorrhage was reported in seven studies, as described above – Harms outcomes, patient Deaths. Between 13 and 19 deaths were related to this type of episode, and there is uncertainty due to the fact that not all deaths cited cause. These events all occurred in the early treatment phase, and were not correlated in the studies with any other adverse events or toxicities.

Non-Hematologic Toxicity

First Line Setting

Grade 3 or 4 hepatic toxic effects were reported more frequently in the ATRA/ATO treatment arm versus the ATRA chemotherapy arm. This difference was statistically significant in the Lo-Coco, 2013[1] trial (63% vs 6%, p<0.001), and more frequent in the Shen, 2004[3] study.

Prolongation of QT interval was reported in Lo-Coco, 2013[1] and in Powell, 2010[2]. The former reported this event occurred in 16% of patients in the ATRA-ATO arm, and in no patients from the ATRA-chemotherapy arm (p<0.001), while the later reported no events at all in either group. Both reported discontinued.

Powell, 2010[2] reported no APL differentiation syndrome in the consolidation phase, and in 37% of cases during induction. Lo-Coco, 2013[1] reported no difference between the two treatment arms in terms of incidence or severity of APL differentiation.

No results were reported for the following outcomes: Neuropathy

Relapse/Refractory Setting

Alimoghaddan, 2011[6] reported APL differentiation in 29% of cases, 3 cases of severe liver dysfunction, one case renal function abnormality, and one case of mild pericardial effusion.

Lazo, 2003[7] reported fatigue, skin rash, and Grade 1 headache in 3, 4, and 5 patients, during induction therapy. In maintenance therapy two patients developed peripheral neuropathy, two patients had grade 1 headache, two patients had fatigue, and one patient had rash. One case of fluid retention, epigastric pain and non-cardiac chest were reported during induction therapy.

Niu, 1999[8] reported 12 skin reactions, 10 gastrointestinal reactions, 15 liver dysfunction episodes, 8 cardiac dysfunction episodes and 5 cases of facial edema and neuropathy from a total 47 treated patients.

Raffoux, 2003[5] reported Differentiation syndrome in thirty five percent of patients (35%), weight gain (60%), ALT/AST elevation ≥2 (45%), hypokalemia (35%), headaches (30%), hyperglycemia (25%), nausea (25%), QT prolongation (25%), diarrhea (20%), peripheral neuropathy (10%), and deep venous thrombosis (10%).

Shen, 1997[10] reported three cases with slight decrease in hemoglobin and platelet counts. Other events were less common and included dermatologic symptoms (26.7%), GI symptoms (26.7%), moderate changes in liver function (13.3%), and EKG changes (13.3%).

Shen, 2001[9] reported main toxicity was impaired hepatic function in 20% and 31.9% of the low and conventional dose groups. In the low dose group other adverse events reported were oral ulcer (n=2) and skin rash (n=2). In the conventional dose group other adverse events reported were skin rash (n=12; GI disturbance (n=5); cardio toxicity (n=8); facial edema (n=5); and neurotoxicity (n=1).

Shigeno, 2005[11] reported that the most frequently occurring adverse event was QT prolongation which was observed in 74% of patients, 15 of those developing ventricular tachycardia requiring antiarrythmic agents. Other adverse events included skin eruptions (50%), nausea & vomiting (35%), liver dysfunction (35%), sensory neuropathy (29%), fluid retention (29%), and diarrhea (18%).

Soignet, 1998[13] listed complications as pulmonary hemorrhage, renal failure, sepsis, graft vs host disease, nonspecific pulmonary infiltrates, and hypotension. Two patients developed

symptoms similar to those of retinoic acid syndrome. Other common reactions were light-headedness during infusion, fatigue, musculoskeletal pain, and mild hyperglycemia.

Soignet, 2001[12] reported symptoms related to retinoic acid syndrome developed in 25% of patients, 42.5% of patients had adverse events related to neuropathy. Sixteen patients had at least one on-study ECG that showed prolonged QT corrected for heart rate (QTc) intervals of more than 500 msec. Two patients had an absolute QT interval of more than 500 msec and one patient who was on telemetry monitoring had an asymptomatic, 7-beat run of torsade de pointes that resolved spontaneously. Other common adverse events were nausea (75%), cough (65%), fatigue (63%), fever (63%), headache (60%), vomiting (58%), tachycardia (55%), diarrhea (53%), and skin rash (43%).

Discontinuation/Dose modification

First Line Setting

In Lo-Coco, 2013[1] there is an extensive description of how dosing was used to control toxic events. ATO and/or ATRA were discontinued in ATRA–arsenic trioxide group (63%) and 4 of 69 patients in the ATRA–chemotherapy group (6%) had grade 3 or 4 hepatic toxic effects during induction or consolidation therapy (for patients in the two groups) or during maintenance therapy (for patients in the ATRA–chemotherapy group) (P<0.001).The study notes that hepatic toxic effects appeared to be manageable with temporary discontinuation of study medication and subsequent dose adjustments.

Dose modifications were not discussed in Powell, 2010[2] and Shen, 2004[3].

Relapsed Refractory Setting

Discontinuation of treatment or dose modification was used in studies as a means to manage patients experiencing major toxicity associated with treatment. Neuropathy, cardiac toxicity, retinoic acid syndrome, APL differentiation, major organ dysfunction were common causes.

Alimoghaddam, 2011[6] reported that in cases of severe liver function abnormalities as well as major renal function impairment medication was discontinued and then resumed after patient stabilization. Further, if WBC increased >10x10^9/L and/or symptoms of APL differentiation syndrome appeared, arsenic trioxide was reduced to 5 mg/day, as a 24 hour slow infusion and in severe cases the drug was temporarily stopped.

Shen, 2001[9] noted that administration of ATO was permanently withdrawn when toxicity grading reached level 3 according to NCI grading criteria. Two patients had doses adjusted during induction therapy due to fluid retention and non-cardiac chest pain.

Three patients in Shen, 1997[10] received low dose chemotherapy which was withdrawn when WBC declined to near 10 X 10^9. No dose discontinuation or reduction was reported during induction therapy.

Two patients in Lazo, 2003[7] developed peripheral neuropathy during maintenance therapy and one of those patients required discontinuation due to toxicity.

Discontinuation was undertaken in the case of severe toxicity in Niu, 1999[8] and Soignet, 1998[13]. No definition of severe toxicity was included alongside these statements but the definition most commonly refers to toxicities with NCI grade >3, 4.

Treatment was discontinued in Shigeno, 2005[11] before the 60 day limit if bone marrow remission achieved, or if substantial toxicity occurred.

Eight patients in Soignet, 2001[12] had therapy interrupted due to retinoic acid syndrome, one patient had dose reduction due to neuropathy, and one patient had ATO therapy discontinued due to ECG abnormalities which subsequently returned to normal.

Three patients in Yanada, 2013[14] discontinued the study due to adverse events (grade 3 skin rash, grade 3 QT prolongation, and grade 4 QT prolongation accompanied by frequent ventricular premature contraction).

There was no discussion of dose discontinuation in Wang, 2004[4].

6.4 Ongoing Trials

Trial Design	Inclusion Criteria	Interventions and Comparators	Outcomes
Study NCT00378365	Diagnosis of APL based on morphological grounds Untreated patients Absence of Hypersensitivity to Arsenic derivatives. No QT interval prolongation or complete atria-ventricular block	ATO Vs. ATRA	**Primary Endpoints:** • EFS **Secondary Endpoints:** • WBC count, Relapse, DFS, MRD,
Study NCT00482833	Newly diagnosed APL by cytomorphology WHO performance status 0- 2 WBC at diagnosis ≤ 10 x 109/L Serum total bilirubin ≤ 3.0 mg/dL (≤ 51µmol/L) Serum creatinine ≤ 3.0 mg/dL (≤ 260 µmol/L)	ATO & ATRA induction and consolidation Vs. ATRA & Idarubicin induction and consolidation, 6-Mercaptopurine (6-MP) and Methotrexate maintenance	**Primary Endpoints:** • EFS **Secondary Endpoints**: • Remission, EFS, OS, hematologic and non-hematologic toxicity, quality of life

7 SUPPLEMENTAL QUESTIONS

No supplemental questions were addressed in this review

8 ABOUT THIS DOCUMENT

This Final Clinical Guidance Report was prepared by the pCODR Leukemia Clinical Guidance Panel and supported by the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding the clinical evidence available on Arsenic Trioxide and its use in the treatment of acute promyelocytic leukemia. Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant pCODR Economic Guidance Report. Details of the pCODR review process can be found on the pCODR website (www.pcodr.ca).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the pCODR Disclosure of Information Guidelines. The manufacturer, as the primary data owner, did not agree to the disclosure of some clinical information, therefore, this information was redacted from this publicly available Guidance Report.

This Final Clinical Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Clinical Guidance Report supersedes the Initial Clinical Guidance Report. Note that no revisions were made in between posting of the Initial and Final Clinical Guidance Reports.

The Leukemia Clinical Guidance Panel is comprised of three medical oncologists .The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package, which is available on the pCODR website (www.pcodr.ca). Final selection of the Clinical Guidance Panels was made by the pERC Chair in consultation with the pCODR Executive Director. The Panel and the pCODR Methods Team are editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

APPENDIX A: LITERATURE SEARCH STRATEGY

First line

Ovid MEDLINE (R), Ovid MEDLINE (R) In-Process & Other Non-Indexed Citations, and Ovid MEDLINE (R) Daily Update.

1. promyelocytic leukemia/ or Leukemia, Promyelocytic, Acute/
2. (acute promyelocytic leuk?emia: or APL:).ti,ab,rn,nm,sh,hw,ot.
3. 1327-53-3.rn,nm.
4. (arsenic trioxide or trisenox).ti,ab,rn,nm,sh,hw,ot.
5. *arsenic trioxide/
6. 1 or 2
7. or/3-5
8. 6 and 7

Human Filter

9. exp animals/
10. exp animal experimentation/
11. exp models animal/
12. exp animal experiment/
13. nonhuman/
14. exp vertebrate/
15. or/9-14
16. exp humans/
17. 15 not 16
18. 8 not 17

Second line (search run without RCT filter)

Ovid MEDLINE (R), Ovid MEDLINE (R) In-Process & Other Non-Indexed Citations, and Ovid MEDLINE (R) Daily Update.

1. promyelocytic leukemia/ or Leukemia, Promyelocytic, Acute/
2. (acute promyelocytic leuk?emia: or APL:).ti,ab,rn,nm,sh,hw,ot.
3. 1327-53-3.rn,nm.
4. (arsenic trioxide or trisenox).ti,ab,rn,nm,sh,hw,ot.
5. *arsenic trioxide/
6. 1 or 2
7. or/3-5
8. 6 and 7

Human Filter

19. exp animals/
20. exp animal experimentation/
21. exp models animal/
22. exp animal experiment/
23. nonhuman/
24. exp vertebrate/
25. or/9-14
26. exp humans/
27. 15 not 16
28. 8 not 17

First Line
Ovid EMBASE

1. promyelocytic leukemia/ or Leukemia, Promyelocytic, Acute/
2. (acute promyelocytic leuk?emia: or APL:).ti,ab,rn,nm,sh,hw,ot.
3. 1327-53-3.rn,nm.
4. (arsenic trioxide or trisenox).ti,ab,rn,nm,sh,hw,ot.
5. *arsenic trioxide/
6. 1 or 2
7. or/3-5
   6 and 7
8. Limit 3 to English language
   Human Filter
9. exp animals/
10. exp animal experimentation/
11. exp models animal/
12. exp animal experiment/
13. nonhuman/
14. exp vertebrate/
15. or/5-10
16. exp humans/
17. exp human experiment/
18. 12 or 13
19. 11 not 14
20. 4 not 15

Second Line (Search conducted without RCT filter)
Ovid EMBASE

21. promyelocytic leukemia/ or Leukemia, Promyelocytic, Acute/
22. (acute promyelocytic leuk?emia: or APL:).ti,ab,rn,nm,sh,hw,ot.
23. 1327-53-3.rn,nm.
24. (arsenic trioxide or trisenox).ti,ab,rn,nm,sh,hw,ot.
25. *arsenic trioxide/
26. 1 or 2
27. or/3-5
    6 and 7

28. Limit 3 to English language
    Human Filter
29. exp animals/
30. exp animal experimentation/
31. exp models animal/
32. exp animal experiment/
33. nonhuman/
34. exp vertebrate/
35. or/5-10
36. exp humans/
37. exp human experiment/
38. 12 or 13
39. 11 not 14
40. 4 not 15

PubMed

1. **((acute promyelocytic leukemia OR APL)) AND ((arsenic trioxide OR ATO) AND publisher[sb])**
   publisher[sb]

3. Literature Search via Cochrane Central Register of Controlled Trials (CENTRAL)

Search terms: Arsenic* OR Arsenic Trioxide* OR ATO* AND Acute Promyelocytic Leukemia OR APL* in Cochrane Central Register of Controlled Trials.

4. Grey Literature Searches

Clinical Trial Registries:

U.S. NIH ClinicalTrials.gov
www.clinicaltrials.gov

Ontario Institute for Cancer. Ontario Cancer trials
www.ontariocancertrials.ca

Search terms: Arsenic, Arsenic Trioxide, ATO, Acute Promyelocytic Leukemia, APL

Select International Agencies:

Food and Drug Administration (FDA):
www.fda.gov

European Medicines Agency (EMA):
www.ema.europa.eu

Search terms: Arsenic, Arsenic Trioxide, ATO, Acute Promyelocytic Leukemia, APL

Conference Abstracts:

American Society of Clinical Oncology (ASCO)
via the *Journal of Clinical Oncology* search portal: http://jco.ascopubs.org/search

Search terms: Arsenic, Arsenic Trioxide, ATO, Acute Promyelocytic Leukemia, APL

American Society of Hematology (ASH)
via the *Journal of American Society of Hematology* search portal:
http://bloodjournal.hematologylibrary.org/site/misc/ASH_Meeting_Abstracts_Info.xhtml

Search terms: Arsenic, Arsenic Trioxide, ATO, Acute Promyelocytic Leukemia, APL

REFERENCES

1. Lo-Coco F, Avvisati G, Vignetti M, Thiede C, Orlando SM, Iacobelli S, et al. Retinoic acid and arsenic trioxide for acute promyelocytic leukemia. New England Journal of Medicine. 2013;369(2):111-21. PubMed PMID: 2013447216.

2. Powell BL, Moser B, Stock W, Gallagher RE, Willman CL, Stone RM, et al. Arsenic trioxide improves event-free and overall survival for adults with acute promyelocytic leukemia: North American Leukemia Intergroup Study C9710. Blood [Internet]. 2010; (19):[3751-7 pp.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/193/CN-00770193/frame.html.

3. Shen ZX, Shi ZZ, Fang J, Gu BW, Li JM, Zhu YM, et al. All-trans retinoic acid/As2O3 combination yields a high quality remission and survival in newly diagnosed acute promyelocytic leukemia. Proceedings of the National Academy of Sciences of the United States of America [Internet]. 2004; (15):[5328-35 pp.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/334/CN-00468334/frame.html.

4. Wang G, Li W, Cui J, Gao S, Yao C, Jiang Z, et al. An efficient therapeutic approach to patients with acute promyelocytic leukemia using a combination of arsenic trioxide with low-dose all-trans retinoic acid. Hematological Oncology. 2004;22(2):63-71. PubMed PMID: 2004454265.

5. Raffoux E, Rousselot P, Poupon J, Daniel MT, Cassinat B, Delarue R, et al. Combined treatment with arsenic trioxide and all-trans-retinoic acid in patients with relapsed acute promyelocytic leukemia. Journal of Clinical Oncology. 2326;21(12):2326-34. PubMed PMID: 2007193221.

6. Alimoghaddam K, Ghavamzadeh A, Jahani M, Mousavi A, Iravani M, Rostami S, et al. Treatment of relapsed acute promyelocytic leukemia by arsenic trioxide in Iran. Archives of Iranian Medicine. 2011;14(3):167-9. PubMed PMID: 2011433115.

7. Lazo G, Kantarjian H, Estey E, Thomas D, O'Brien S, Cortes J. Use of arsenic trioxide (As2O3) in the treatment of patients with acute promyelocytic leukemia: the M. D. Anderson experience. Cancer. 2218;97(9):2218-24. PubMed PMID: 12712474.

8. Niu C, Yan H, Yu T, Sun S, Liu JX, Xiu-Song L, et al. Studies on treatment of acute promyelocytic leukemia with arsenic trioxide: Remission induction, follow-up, and molecular monitoring in 11 newly diagnosed and 47 relapsed acute promyelocytic leukemia patients. Blood. 3315;94(10):3315-24. PubMed PMID: 1999398422.

9. Shen Y, Shen ZX, Yan H, Chen J, Zeng XY, Li JM, et al. Studies on the clinical efficacy and pharmacokinetics of low-dose arsenic trioxide in the treatment of relapsed acute promyelocytic leukemia: A comparison with conventional dosage. Leukemia. 2001;15(5):735-41. PubMed PMID: 2001194493.

10. Shen ZX, Chen GQ, Ni JH, Li XS, Xiong SM, Qiu QY, et al. Use of arsenic trioxide (As2O3) in the treatment of acute promyelocytic leukemia (APL): II. Clinical efficacy and pharmacokinetics in relapsed patients. Blood. 3354;89(9):3354-60. PubMed PMID: 9129042.

11. Shigeno K, Naito K, Sahara N, Kobayashi M, Nakamura S, Fujisawa S, et al. Arsenic trioxide therapy in relapsed or refractory Japanese patients with acute promyelocytic leukemia: Updated outcomes of the phase II study and postremission therapies. International Journal of Hematology. 2005;82(3):224-9. PubMed PMID: 2005492875.

12. Soignet SL, Frankel SR, Douer D, Tallman MS, Kantarjian H, Calleja E, et al. United States multicenter study of arsenic trioxide in relapsed acute promyelocytic leukemia. Journal of Clinical Oncology. 3852;19(18):3852-60. PubMed PMID: 2001330944.

13. Soignet SL, Maslak P, Wang ZG, Jhanwar S, Calleja E, Dardashti LJ, et al. Complete remission after treatment of acute promyelocytic leukemia with arsenic trioxide. New England Journal of Medicine. 1341;339(19):1341-8. PubMed PMID: 1998376756.

14. Yanada M, Tsuzuki M, Fujita H, Fujimaki K, Fujisawa S, Sunami K, et al. Phase 2 study of arsenic trioxide followed by autologous hematopoietic cell transplantation for relapsed acute promyelocytic leukemia. Blood. 3095;121(16):3095-102. PubMed PMID: 23412094.

15. Breccia M, Minotti C, Latagliata R, Finsinger P, Ammatuna E, Sica S, et al. Arsenic trioxide alone or combined to retinoic acid for relapsed acute promyelocytic leukemia. Haematologica. 2009;Conference:42 Congress of the Italian Society of Hematology Milano Italy. Conference Start: 20091018 Conference End: 21. Conference Publication: (var.pagings). 94 (pp 69). PubMed PMID: 70081684.

16. Thomas X, Dombret H, Cordonnier C, Pigneux A, Gardin C, Guerci A, et al. Treatment of relapsing acute promyelocytic leukemia by all-trans retinoic acid therapy followed by timed sequential chemotherapy and stem cell transplantation. Leukemia. 2000;14(6):1006-13. PubMed PMID: 2000210914.

17. Paulson C, Serebrin A, Turner D, Bergeron J, Couban S, Jones D, et al. EPIDEMIOLOGY AND OUTCOMES OF APL IN A LARGE POPULATION BASED CANADIAN COHORT. Hematologica 2012 June 2012;97:67.

18. Iland HJ, Bradstock K, Supple SG, Catalano A, Collins M, Hertzberg M, et al. All-trans-retinoic acid, idarubicin, and IV arsenic trioxide as initial therapy in acute promyelocytic leukemia (APML4). Blood. 2012 23 Aug;120(8):1570-80. PubMed PMID: 2012502750.

19. Tallman MS, Nabhan C, Feusner JH, Rowe JM. Acute promyelocytic leukemia: evolving therapeutic strategies. Blood. 2002;99(3):759-67. PubMed PMID: 11806975.

20. Center for Drug Evaluation and Research, U.S. Food and Drug Administration. Label review [Internet]. In:Trisenox (arsenic tioxide). Company: Cephalon, Inc. Application no.: 021248. Approval date07/23/2010 . Rockville (MD): The Center; 2013 [cited 2013 November 13]. (FDA drug approval package). Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021248s008s009lbl.pdf

21. European medicines Agency, Clinical Particulars[Internet]. In: Arsenic Trioxide (Trisenox) injection. Company: TEVA Pharma B.V.,Netherlands. Agency Product : EMEA/H/C/000388. Date of Marketing Authorisation: 05/03/2002. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR__Product_Information/human/000388/WC500042844.pdf

22. Trisenox (Arsenic Trioxide) 10 mg/10 mL (1 mg/mL) ampoule [product monograph]. Montreal (QC): Lundbeck Canada Inc.; 2014 January 2.

23. Tallman MS, Altman JK. How I treat acute promyelocytic leukemia. Blood. 2009 10 Dec;114(25):5126-35. PubMed PMID: 19797519.

24. Ribeiro RC, Rego E. Management of APL in developing countries: epidemiology, challenges and opportunities for international collaboration. Hematology / the Education Program of the American Society of Hematology. 2006;American Society of Hematology. Education Program.:162-8. PubMed PMID: 17124056.

25. Wang H, Chen XY, Wang BS, Rong ZX, Qi H, Chen HZ. The efficacy and safety of arsenic trioxide with or without all-trans retinoic acid for the treatment of acute promyelocytic leukemia: A meta-analysis. Leukemia Research. 1170;35(9):1170-7. PubMed PMID: 2011437252.

26. Wang H, Rong ZX, Qi H, Zhang Y, Wang BS, Chen HZ. Focused Conference Group: P16 - Natural products: Past and future? The effectiveness and safety of arsenic trioxide with and without all-trans retinoic acid in the treatment of acute promyelocytic leukaemia: A meta-analysis. Basic and Clinical Pharmacology and Toxicology. 2010;Conference:16th World Congress of Basic and Clinical Pharmacology - WorldPharma 2010

Copenhagen Denmark. Conference Start: 20100717 Conference End: 23. Conference Publication: (var.pagings). 107 (pp 646). PubMed PMID: 70224311.

27. Xu SN, Chen JP, Liu JP, Xia Y. Arsenic trioxide in combination with all-trans retinoic acid for acute promyelocytic leukemia: A systematic review and meta-analysis. Journal of Chinese Integrative Medicine. 1023;7(11):1023-34. PubMed PMID: 2010034056.

28. Au W-Y, Kumana CR, Lee HKK, Lin S-Y, Liu H, Yeung DYM, et al. Oral arsenic trioxide–based maintenance regimens for first complete remission of acute promyelocytic leukemia: a 10-year follow-up study. Blood. 2011 December 15, 2011;118(25):6535-43.

29. Lou Y, Jin J. Long-Term Efficacy of Low-Dose All-Trans Retinoic Acid Plus Individually Adapted Chemotherapy Induction Followed by Arsenic Trioxide Based Post-Remission Therapy in Adults with Newly Diagnosed Acute Promyelocytic Leukemia. ASH Annual Meeting Abstracts. 2012 December 6, 2012;120(21):1480.

30. Mathews V, George B, Jijina F, Ross C, Nair R, Apte S. Final analysis of a multi-center randomized controlled trial (IAPLSG04) to study the optimal duration of arsenic trioxide maintenance therapy in the treatment of newly diagnosed acute promyelocytic leukemia [abstract no. 426]. Blood [Internet]. 2011; (21). Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/024/CN-00841024/frame.html.

31. Mathews V, George B, Jijina F, Ross C, Nair R, Apte S, et al. Single agent arsenic trioxide regimen for the treatment of newly diagnosed acute promyelocytic Leukemia: Initial results of a multicenter randomized controlled study from india to study the optimal duration of arsenic trioxide maintenance therapy (IAPLSG04). Blood. 2009 20 Nov;114 (22). PubMed PMID: 70247303.

32. Powell BL, Moser BK, Stock W, Gallagher RE, Willman CL, Stone RM, et al. Adding mercaptopurine and methotrexate to alternate week ATRA maintenance therapy does not improve the outcome for adults with Acute Promyelocytic Leukemia (APL) in first remission: Results from North American leukemia intergroup trial C9710. Blood. 2011 18 Nov;118 (21). PubMed PMID: 70772369.

33. Powell BL, Tallman MS, Couban S, Coutre SE. Phase III Randomized Study of Tretinoin, Cytarabine, and Daunorubicin With or Without Arsenic Trioxide as Induction/Consolidation Therapy Followed by Intermittent Tretinoin With or Without Mercaptopurine and Methotrexate as Maintenance Therapy in Patients With Previously Untreated Acute Promyelocytic Leukemia. National Institutes of Health, ClinicalTrials Gov [http://wwwclinicaltrialsgov] [Internet]. 2003. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/439/CN-00455439/frame.html.

34. Ravandi F, Estey EH, Appelbaum FR, Lo-Coco F, Schiffer CA, Larson RA, et al. Gemtuzumab ozogamicin: Time to resurrect? Journal of Clinical Oncology. 2012 10 Nov;30(32):3921-3. PubMed PMID: 2012680566.

35. Zhu HH, Wu DP, Jin J, Li JY, Ma J, Wang JX, et al. Oral Tetra-Arsenic Tetra-Sulfide Formula Versus Intravenous Arsenic Trioxide As First-Line Treatment of Acute Promyelocytic Leukemia: A Multicenter Randomized Controlled Trial. J Clin Oncol. 2013 Nov 20;31(33):4215-21.

36. Zhu ZH, Wu DP, Jin J, Li JY, Ma J, Wang J, et al. Oral realgar-indigo naturalis formula achieved comparably high rate of remission and survival to intravenous arsenic trioxide as a front-line treatment in newly diagnosed acute promyelocytic leukemia: A multi-center randomized trial apl07. Blood. 2012 16 Nov;120 (21). PubMed PMID: 70960280.

37. Ades L, Raffoux E, Chevret S, Pigneux A, Thomas X, Bordessoule D, et al. Arsenic Trioxide (ATO) in the consolidation treatment of newly diagnosed APL - First interim analysis of a randomized trial (APL 2006) by the French Belgian Swiss APL Group. Blood. 2010 19 Nov;116 (21). PubMed PMID: 70774141.

38. Powell BL, Moser B, Stock W, Gallagher RE, Willman CL, Stone RM, et al. Preliminary Results from the North American Acute Promyelocytic Leukemia (APL) Study C9710. ASH Annual Meeting Abstracts. 2006 December 13, 2006;108(11):566.

39. Zhang L, Zhu X, Zou Y, Chen Y, Chen X. Effect of arsenic trioxide on the treatment of children with newly diagnosed acute promyelocytic leukemia in China. International Journal of Hematology [Internet]. 2011; (2):[199-205 pp.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/471/CN-00787471/frame.html.

40. Huang WX, Li R. Clinical observation on the efficacy of the treatment with combination of all-trans retinoic acid and arsenic trioxide in 50 cases of newly diagnosed acute promyelocyte leukemia. Journal of Leukemia and Lymphoma. 2011 May;20(5):282-5. PubMed PMID: 2011490308.

41. Zhang X, Yang L, Qiao Z. An analysis of the therapeutic effects and reactions in treating acute promyelocytic leukemia with intravenous arsenic trioxide or all-trans retinoic acid. [Chinese]. Zhonghua nei ke za zhi [Chinese journal of internal medicine]. 1999 Feb;38(2):113-5. PubMed PMID: 11798639.

42. Rossini R, Miccolis IR, Ferrario A, Vergani C, Avanzi G, Cantoni P, et al. Treatment of relapsing acute promyelocytic leukemia (APL) with arsenic trioxide +- ALL-trans retinoic acid (ATRA): the french as98 study [abstract]. Hematology Journal [Internet]. 2000; (Suppl 1):[23 p.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/683/CN-00580683/frame.html.

43. Asou N. Arsenic trioxide in the treatment of relapsed and refractory acute promyelocytic leukemia. Internal Medicine. 2005;44(8):775-6. PubMed PMID: 2005405031.

44. Aribi A, Kantarjian HM, Estey EH, Koller CA, Thomas DA, Kornblau SM, et al. Combination therapy with arsenic trioxide, all-trans retinoic acid, and gemtuzumab ozogamicin in recurrent acute promyelocytic leukemia. Cancer. 1355;109(7):1355-9. PubMed PMID: 2007150622.

45. Hu J, Shen ZX, Sun GL, Chen SJ, Wang ZY, Chen Z. Long-term survival and prognostic study in acute promyelocytic leukemia treated with all-trans-retinoic acid, chemotherapy, and As2O3: an experience of 120 patients at a single institution. International journal of hematology. 1999;70(4):248-60. PubMed PMID: 10643151.

46. Chen Y, Kantarjian H, Wang H, Cortes J, Ravandi F. Acute promyelocytic leukemia: A population-based study on incidence and survival in the United States, 1975-2008. Cancer. 5811;118(23):5811-8. PubMed PMID: 2012680214.

47. Cohen MH, Hirschfeld S, Honig SF, Ibrahim A, Johnson JR, O'Leary JJ, et al. Drug approval summaries: Arsenic trioxide, tamoxifen citrate, anastrazole, paclitaxel, bexarotene. Oncologist. 2001;6(1):4-11. PubMed PMID: 2001068575.

48. Henney JE. From the Food and Drug Administration. JAMA : the journal of the American Medical Association. 2178;284(17). PubMed PMID: 11056574.

49. Wang GJ, Li W, Cui JW, Gao SJ, Yao C, Jiang ZY, et al. Therapeutic effects of combination of arsenic trioxide with low-dose all-trans retinoic acid on induction of remission acute promyeloeytic leukemia. National Medical Journal of China. 1093;85(16):1093-6. PubMed PMID: 2005280513.

50. Schumi J, Wittes JT. Through the looking glass: understanding non-inferiority. Trials. 2011;12:106. PubMed PMID: 21539749.

51. Snapinn SM. Noninferiority trials. Current Controlled Trials in Cardiovascular Medicine. 2000;1(1):19-21. PubMed PMID: 2001103835.

52. Pan-Canadian Oncology Drug Review Manufacturer Submission: Arsenic Trioxide (Trisenox); Company: Lundbeck Canada. Montreal QCLC.