NHS England evidence review:

Arsenic trioxide with all trans retinoic acid for high-risk acute promyelocytic leukaemia

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Contents

1. Introduction

This evidence review examines the clinical effectiveness, safety and cost effectiveness of arsenic trioxide (ATO) in combination with all trans retinoic acid (ATRA) compared to chemotherapy in combination with ATRA in patients with newly diagnosed high-risk acute promyelocytic leukaemia (APML).

ATO may be used in the treatment of APML. It can be administered using either oral or intravenous routes, alongside treatment with ATRA. ATO and ATRA can be given in combination with idarubicin chemotherapy during the induction phase only. The comparator is chemotherapy in combination with ATRA. This is usually anthracycline chemotherapy (primarily idarubicin, but could also include daunorubicin, etoposide, doxorubicin or mitoxantrone). Both the intervention and comparison of interest may be given alongside best supportive care, for example with hydroxycarbamide, prednisolone or dexamethasone.

In addition, the review scope included the identification of possible subgroups of patients within the included studies who might benefit from treatment with ATO in combination with ATRA more than others, as well as the criteria used by the included studies to confirm a diagnosis of newly diagnosed high-risk APML, and the treatment regimens used in the included studies to treat high-risk APML.

2. Executive summary of the review

This evidence review examines the clinical effectiveness, safety and cost effectiveness of arsenic trioxide (ATO) in combination with all trans retinoic acid (ATRA) compared to chemotherapy in combination with ATRA in patients with newly diagnosed high-risk (HR) acute promyelocytic leukaemia (APML). The searches for evidence published since January 2013 were conducted on 14 September 2023 and identified 844 references. The titles and abstracts were screened, and 53 full text papers were obtained and assessed for relevance.

Three papers were identified for inclusion. One paper was a randomised controlled trial (RCT) conducted in three centres in China, from which only a subgroup of the intervention arm (21 patients with newly diagnosed HR APML from a total of 62 patients in the intervention arm) could be included because the comparator arm of ATO+ATRA+chemotherapy did not match the PICO specification. One paper was a non-randomised non-inferiority trial with historical controls, from which only a subgroup of the intervention arm (56 patients with newly diagnosed HR APML from a total of 154 patients in the intervention arm) could be included because the historical controls did not receive ATO during induction and received ATO+chemotherapy during consolidation and maintenance. This non-randomised non-inferiority trial was conducted across 85 centres in the USA, Canada and Australia. These two trials have been included as noncomparative evidence because the comparators used in the papers did not match the PICO specification. The final included paper was a small retrospective case series (ten patients with HR APML who had survived induction, of whom nine received ATO+ATRA) conducted in the USA. Therefore, only non-comparative evidence was included in the review. Outcomes were reported at two years in the RCT and non-randomised non-inferiority trial, and median follow-up in the case series was 38 months.

No cost effectiveness studies suitable for inclusion in this evidence review were identified. **In terms of clinical effectiveness:**

- **Overall survival (critical outcome).** Two studies provided very low certainty noncomparative evidence that between 85% and 100% of people with HR newly diagnosed APML treated with ATO+ATRA (+idarubicin in one study) during induction and ATO+ATRA during consolidation were still alive at two years follow-up. There was very low certainty evidence from one small case series that 100% of patients with HR APML who survived induction with ATO+ATRA+idarubicin and received ATO+ATRA during consolidation were still alive at a median of 38 months follow-up.

- **Event-free survival (critical outcome).** Two studies provided very low certainty noncomparative evidence that between 85% and 96.4% of people with HR newly diagnosed APML treated with ATO+ATRA (+idarubicin in one study) during induction and ATO+ATRA during consolidation were still alive at two years follow-up without having experienced an event such as failure to achieve haematologic/molecular remission, relapse or death.

- **Disease-free survival or remission (critical outcome).** Three studies provided very low certainty non-comparative evidence about the disease-free survival rate. Following induction and consolidation with ATO+ATRA, 85% of patients with HR newly diagnosed APML had survived without relapse at two years. For HR newly diagnosed APML patients treated with ATO+ATRA+idarubicin during induction and ATO+ATRA during consolidation, 3.9% had relapsed within two years. There was very low certainty

evidence from one small case series that no patients with HR APML who survived induction with ATO+ATRA+idarubicin and were treated with ATO+ATRA during consolidation had relapsed at a median of 38 months follow-up.

- **Quality of life (important outcome).** No evidence was identified for this outcome.
- **Hospitalisation (important outcome).** One study provided very low certainty noncomparative evidence that the median hospital stay during induction with ATO+ATRA for people with HR newly diagnosed APML was 29 days, with a range of 16 to 39 days.
- **Activities of daily living (important outcome).** No evidence was identified for this outcome.

In terms of safety:

- **Adverse events during induction phase.** Two studies provided very low certainty noncomparative evidence about adverse events during the induction phase. Median duration of IV antibiotics during induction with ATO+ATRA was the only adverse event reported separately for the subgroup of patients with HR newly diagnosed APML in one arm of one RCT. Symptoms of differentiation syndrome were experienced during the induction phase (with ATO+ATRA+idarubicin) by 30% of patients in a subgroup of the intervention arm of one non-randomised non-inferiority trial. Whilst 18% of patients in that study had no adverse events during induction, 59% of patients had a prolonged ECG QT corrected interval during induction.
- **Adverse events during consolidation phase.** One study provided very low certainty non-comparative evidence about adverse events. Between 40% and 62% of patients experienced no adverse events during consolidation cycles. The proportion of patients with a prolonged ECG QT corrected interval ranged from 32% to 55% across consolidation cycles. None of the studies reported on longer-term adverse effects.

In terms of cost effectiveness:

- No evidence was identified for cost effectiveness.

In terms of subgroups:

- No evidence was identified regarding any subgroups of patients that would benefit more from treatment with ATO+ATRA.

Definition of high-risk APML:

- The non-randomised non-inferiority trial defined high-risk APML as a white blood cell (WBC) count of 10000/μL or higher, and the RCT similarly categorised high-risk APML as a WBC of at least 10×10^9/L.
- The retrospective case series assigned patients to risk groups based on laboratory assessment prior to receiving ATRA, with no further details of definition of high-risk

APML. Diagnosis was confirmed by fluorescence in situ hybridization (FISH) analysis for the promyelocytic leukaemia/retinoic acid receptor alpha (PML/RARA) gene fusion.

Treatment regimens used to treat high-risk APML:

- In the non-randomised non-inferiority trial, induction therapy included twice daily oral ATRA (12.5mg/m^2 per dose), and daily intravenous ATO (0.15mg/kg) for 28 to 70 days. Patients with high-risk APML also received four doses of idarubicin, 12.0mg/m^2 per dose (patients with body surface area <0.6m^2 received 0.4mg/kg per dose) on days 1, 3, 5,

  and 7 as well as empirical therapy for differentiation syndrome with twice daily dexamethasone, 2.5mg/m^2, on days 1 to 14. All patients received four cycles (three cycles of eight weeks' duration and one cycle of four weeks' duration) of ATO+ATRA consolidation therapy and no maintenance therapy.

- In the intervention arm of the RCT, high-risk patients received ATRA (40mg/d (body surface area < 1.5m^2) or 60mg/d (body surface area ≥ 1.5m^2) (20 to 45mg/m^2/d) in divided doses) and ATO (0.15mg/kg/d) for induction, consolidation, and maintenance. Both ATO and ATRA were administered for two weeks every four weeks in the consolidation and maintenance therapy. Synchronous administration of mannitol and ATO was used to prevent central nervous system leukaemia in high-risk patients during consolidation and maintenance phase. Hydroxyurea was given to control the WBC count during the induction phase, at a mean dose of 36.03g (range 19.5 to 59g).

- The retrospective case series incorporated idarubicin (age adjusted) with ATRA (45 mg/m^2/day) + ATO (0.15 mg/kg/day) for induction. Consolidation was stated to be as per APL0406 regimen[1], with no further details.

Please see the results table (section 5) in the review for further details of outcomes and definitions.

Limitations

No comparative evidence was available for the clinical effectiveness or safety of ATO+ATRA compared to ATRA+chemotherapy for the treatment of high-risk APML. Certainty about the evidence for all critical and important outcomes was very low when assessed using modified GRADE. Only a subgroup of the intervention arm from the RCT and a subgroup of one arm of the non-randomised non-inferiority trial met the inclusion criteria for this review; the RCT active comparator arm and the historical controls used in the non-randomised non-inferiority trial had received chemotherapy alongside ATO during consolidation and maintenance phases (and had not received ATO during induction in the non-randomised non-inferiority trial), so were not in scope for this review. In the retrospective case series, one of the ten patients had not received ATO, so was excluded from the review. The studies' small sample sizes for the patients of relevance to this review (ranging from nine to 56 patients) were another limitation. It was not clear whether there was consecutive or complete inclusion of participants in the nonrandomised non-inferiority trial or the retrospective case series, so selection bias may have been introduced. The retrospective case series only included patients who had survived induction. In terms of comparability of the studies, patients in the ATO+ATRA arm of the RCT did not receive

[1] The reference provided by Shah et al 2020 for the APL0406 regimen describes this as ATRA 45 mg/m2/day for 15 days, starting on weeks 0, 4, 8, 12, 16, 20 and 24 of the consolidation phase, with ATO 0.15 mg/kg/day 5 days per week starting on weeks 0, 8, 16 and 24.

idarubicin during induction, whereas those in the non-inferiority trial and the retrospective case series did receive idarubicin alongside ATO+ATRA during induction. Another difference was that the participants in the non-randomised, non-inferiority trial were predominantly children, with all being under the age of 21, whereas the majority of participants in the RCT and case series were adults. None of the studies were conducted in the UK so their applicability to the patients seen in clinical practice in England is uncertain.

No studies reported quality of life or activities of daily living, and only the RCT reported hospitalisation (as the median duration of hospital stay during induction). In terms of safety, the RCT only reported deaths and use of intravenous antibiotics during the induction phase separately for the high-risk patients. The non-randomised non-inferiority trial reported adverse events during the induction and consolidation treatment phases. The retrospective case series did not report on safety. The studies did not have sufficient follow-up time to present evidence for the longer-term safety outcomes of interest, such as impact on fertility and cardiotoxicity. No evidence was identified for the cost effectiveness of ATO+ATRA compared to ATRA+chemotherapy in patients with high-risk newly diagnosed APML.

Conclusion

Very low certainty, non-comparative data was available from three studies for the critical outcomes of overall survival and disease-free survival or remission, and from two studies for the critical outcome of event-free survival. Two-year survival and disease-free survival rates of between 85% and 100% were reported by the studies, with two-year event-free survival rates of between 85% and 96%. Very low certainty, non-comparative evidence was available from one study for the important outcome hospitalisation (only reported for the induction period). None of the studies reported the important outcomes quality of life or activities of daily living. In terms of safety, only very low certainty evidence was available from two studies during the induction phase, and from one study during the consolidation phase. During the consolidation cycles (when no chemotherapy was given) between 40% and 62% of patients experienced no adverse events. No evidence on cost effectiveness was identified.

No comparative evidence was available, so it is not possible to draw reliable conclusions about the clinical effectiveness, safety or cost effectiveness of ATO+ATRA compared to ATRA+chemotherapy in people with high-risk APML.

3. Methodology

Review questions

The review question(s) for this evidence review are:

1. In high-risk acute promyelocytic leukaemia what is the clinical effectiveness of arsenic trioxide and all trans retinoic acid compared with current standard care?
2. In high-risk acute promyelocytic leukaemia what is the safety of arsenic trioxide and all trans retinoic acid compared with current standard care?
3. In high-risk acute promyelocytic leukaemia what is the cost effectiveness of arsenic trioxide and all trans retinoic acid compared with current standard care?
4. From the evidence selected, are there any subgroups of patients that may benefit from arsenic trioxide and all trans retinoic acid more than the wider population of interest?
5. From the evidence selected, what are the criteria used by the research studies to define high-risk acute promyelocytic leukaemia?
6. From the evidence selected, what were the treatment regimens used to treat high-risk acute promyelocytic leukaemia?

See Appendix A for the full PICO document.

Review process

The methodology to undertake this review is specified by NHS England in its 'Guidance on conducting evidence reviews for Specialised Services Commissioning Products' (2020).

The searches for evidence were informed by the PICO document and were conducted on 14 September 2023.

See Appendix B for details of the search strategy.

Results from the literature searches were screened using their titles and abstracts for relevance against the criteria in the PICO document. Full text of potentially relevant studies were obtained and reviewed to determine whether they met the inclusion criteria for this evidence review.

See Appendix C for evidence selection details and Appendix D for the list of studies excluded from the review and the reasons for their exclusion.

Relevant details and outcomes were extracted from the included studies and were critically appraised using a checklist appropriate to the study design. See Appendices E and F for individual study and checklist details.

The available evidence was assessed by outcome for certainty using modified GRADE. See Appendix G for GRADE profiles.

4. Summary of included studies

Three papers were identified for inclusion (Kutny et al 2022, Shah et al 2020, Wang et al 2022). One paper was a randomised controlled trial (Wang et al 2022), from which only a subgroup of in-scope patients from the intervention arm (n=21 patients) could be included. The comparator arm of ATO+ATRA+chemotherapy did not match the PICO specification. Therefore, only noncomparative data is available from this RCT. The study by Kutny et al 2022 was a nonrandomised non-inferiority trial with historical controls. Only a subgroup of in-scope patients from the intervention arm (n=56 patients) could be included. The historical controls used in the trial did not match the PICO specification as they did not receive ATO during induction and received ATO+chemotherapy during consolidation and maintenance. Therefore, only noncomparative data is available from this non-randomised non-inferiority trial. The final included paper (Shah et al 2020) was a small retrospective case series (n=10 patients) from which nine in-scope patients who received ATO+ATRA could be included.

No cost effectiveness studies suitable for inclusion in this evidence review were identified.

Table 1 provides a summary of the included studies and full details are given in. Appendix E.

Table 1: Summary of included studies

Study	Population	Intervention and comparison	Outcomes reported
Kutny et al 2022 Intervention arm of a nonrandomised, non-inferiority trial with historical controls (comparator not in scope, so included as noncomparative study) 85 centres in Australia, Canada, USA	56 patients aged 1 to 21 with HR[a] newly diagnosed APML (56/154, 36.4% of intervention arm) Median age 12.6 years (range 1.1 to 20.8 years) Median WBC x1000/µL: 41.1 (range 10.2 to 255.1) No subgroups reported	**Intervention** Induction: ATO+ATRA+idarubicin • Twice daily oral ATRA 12.5mg/m^2 per dose, and daily intravenous ATO, 0.15mg/kg; for at least 28 days • 4 doses of idarubicin, 12.0 mg/m^2 per dose (patients with body surface area <0.6m^2 received 0.4mg/kg per dose) on days 1, 3, 5, and 7 • Empirical therapy for differentiation syndrome (twice daily dexamethasone, 2.5mg/m^2 on days 1 to 14 Consolidation: ATO+ATRA intermittently during 4 cycles (3 8-week cycles and 1 4-week cycle) **Comparators** None[d]	**Critical outcomes** • Overall survival at 2 years • Event-free survival[b] at 2 years • Disease-free survival[c] or remission at 2 years **Important outcomes** Median follow-up: 22.8 months (range 0 to 47.7 months) • Safety: early death (during induction) and adverse events
Shah et al 2020 Retrospective case series	9 patients with HR APML[e] who survived induction and subsequently received consolidation with ATO and ATRA (9/10, 90% of whole case series)	**Interventions** Induction: ATO (0.15 mg/kg/day)+ATRA (45 mg/m^2/day)+idarubicin (age adjusted)[f]	**Critical outcomes** Reported at median 38 months (range 14 to 63) from diagnosis • Overall survival • Disease-free survival or remission[h]

Study	Population	Intervention and comparison	Outcomes reported
USA, single centre	Median age: 44.5 (range 17 to 77) years Median WBC count (x 10^3 /$mm^{3)}$: 42.3 (range 14.7 to 167.5) No subgroups reported	Consolidation: ATO+ATRA as per APL0406 regimen[g] No maintenance phase **Comparators** None	
Wang et al 2022 Intervention arm of a RCT (comparator not in scope, so included as noncomparative study) 3 centres in China	21 patients with HR[i] newly diagnosed APML (21/62, 33.9% of the intervention arm) Median age of whole intervention arm (n=62) 41 years (range 15 to 69) No subgroups reported	**Interventions** Induction: ATO+ATRA (until HCR), consolidation (until MCR), and maintenance[j] ATRA: 40 mg/d (BSA < $1.5m^2$) or 60mg/d (BSA ≥ $1.5m^2$) (20 to 45mg/m^2/d) in divided doses ATO: 0.15 mg/kg/d[k] Consolidation and maintenance: Both ATO and ATRA were administered for 2 weeks every 4 weeks. Synchronous administration of mannitol and ATO was used to prevent central nervous system leukaemia in HR patients during consolidation and maintenance phase **Comparators** None[l]	**Critical outcomes** • Overall survival at 2 years • Event-free survival[m] at 2 years • Disease-free survival[n] or remission at 2 years **Important outcomes** • Hospitalisation (during induction[o]) • Safety (IV antibiotics during induction; deaths during induction)

Abbreviations
APML: acute promyelocytic leukaemia; ATO: arsenic trioxide; ATRA: all trans retinoic acid; BSA: body surface area; CT: chemotherapy; HCR: haematological complete remission; HR: high risk; IV: intravenous; MCR: molecular complete remission; RCT: randomised controlled trial; WBC: white blood cell count

Footnotes [a] HR defined as WBC count ≥10000/μL.

[b] Kutny et al 2022 describe event-free survival as: "time from study entry until failure to achieve haematologic complete remission or haematologic complete remission with incomplete haematologic recovery by day 70 of induction therapy; time from study entry until failure to achieve molecular remission after consolidation cycle 2, including consolidation therapy, if needed, for those with molecular residual disease; or time from study entry until relapse or death".

[c] Kutny et al 2022 report disease-free survival as APL relapse, defined as: "time from the end of induction therapy (for patients in haematologic complete remission or haematologic complete remission with incomplete haematologic recovery) to relapse or death, in which deaths without relapse were considered competing events. Disease relapse was defined as the reappearance of promyeloblasts or abnormal promyelocytes (>5%) or 2 consecutive positive results for the presence of PML-RARα on qPCR tests of the bone marrow."

[d] Historical controls received CT beyond induction and did not receive ATO during induction, so were not in scope for this review. [e] Shah et al 2020 do not specify whether this was newly diagnosed APML. Assignment to risk group was based on laboratory assessment prior to receiving ATRA. [f] One patient in Shah et al 2020 did not receive ATO during induction and one patient did not receive idarubicin. [g] The reference provided by Shah et al 2020 for the APL0406 regimen describes this as ATRA 45mg/m^2/day for 15 days, starting on weeks 0, 4, 8, 12, 16, 20 and 24 of the consolidation phase, with ATO 0.15mg/kg/day 5 days per week starting on weeks 0, 8, 16 and 24. [h] Described as number of patients with relapse. [i] HR defined as WBC ≥10 × 109/L. [j] Route of administration not described by Wang et al 2022.

[k] One person in Wang et al 2022 received ATRA plus Realgar-Indigo naturalis formula (RIF) due to patient choice. [l] RCT comparator arm was ATRA-ATO-CT, so not in scope. [m] Wang et al 2022 define event-free survival as: "time from diagnosis to first event, including death during induction therapy, failure to achieve remission, death during remission, relapse at any site, or the development of second malignant neoplasm. [n] Wang et al 2022 define disease-free survival as: "time from haematological complete remission (HCR) to either haematological or molecular relapse or death from APL".

Study	Population	Intervention and comparison	Outcomes reported
[o] Induction phase until HCR. Time to HCR was not specified for HR patients. For the whole intervention arm (n=62), median time to HCR was 32.5 days (14-54 days).			

5. Results

In high-risk acute promyelocytic leukaemia what is the clinical effectiveness and safety of arsenic trioxide and all trans retinoic acid compared with current standard care?

Outcome	Evidence statement
Clinical Effectiveness	
Critical outcomes	
Overall survival **Certainty of evidence:** Very low	This outcome is important to patients as patients with HR APML have a higher mortality rate due to risk of fatal haemorrhage. Improved overall survival is an important marker of effective treatment, although it does not provide information about a patient's health and wellbeing during that time. In total, one subgroup of the intervention arm of an RCT, one subgroup of the intervention arm of a non-randomised non-inferiority trial and one retrospective case series provided evidence relating to overall survival at either two years or 38 months follow-up. The RCT intervention arm included people with either non-HR or HR newly diagnosed APML, with a median age of 41 years (range 15 to 69). Only those with HR APML are included here. The intervention arm of the nonrandomised non-inferiority trial included people with either standard-risk or HR newly diagnosed APML; only those with HR APML are included here (median age 12.6 years, range 1.1 to 20.8). The retrospective case series included 10 people with HR APL who had survived induction treatment. Only nine of these received ATO and are included here. 2-year overall survival rate • One subgroup of the intervention arm of an RCT (Wang et al 2022) showed that, following induction and consolidation with ATO+ATRA, the 2year overall survival rate was 85% (18/21 patients[2]). One subgroup of the intervention arm of a non-randomised non-inferiority trial (Kutny et al 2022) showed that, following induction treatment with ATO+ATRA+idarubicin and consolidation with ATO+ATRA, the 2-year overall survival rate was 100% (90% CI 93.0% to 100%; 56/56 patients). **(VERY LOW)** Overall survival at median 38 months • One retrospective case series (Shah et al 2020) showed that 100% (9/9) of patients with HR APML who survived induction with ATO+ATRA+idarubicin and received ATO+ATRA during consolidation were still alive at a median of 38 months follow-up (range 14 to 63 months). **(VERY LOW)** **Two studies provided very low certainty non-comparative evidence that between 85% and 100% of people with HR newly diagnosed APML treated with ATO+ATRA (+idarubicin in one study) during induction and ATO+ATRA during consolidation were still alive at two years follow-up. There was very low certainty evidence from one small case series that 100% of patients with HR APML who survived induction with ATO+ATRA+idarubicin and received ATO+ATRA during consolidation were still alive at a median of 38 months follow-up.**

[2] In addition to two deaths in the Wang et al 2022 study, one person did not receive any post-remission therapy and disease monitoring.

Event-free survival **Certainty of evidence:** Very low	This outcome is important to patients because it represents the time during which their disease is not progressing. Stable disease might represent longer survival and disease stability may result in patients experiencing fewer symptoms from the disease itself. It can be determined sooner than overall survival outcome measures.

Outcome	Evidence statement
	In total, one subgroup of the intervention arm of an RCT and one subgroup of the intervention arm of a non-randomised non-inferiority trial provided evidence relating to overall survival at two years. The RCT arm included people with either non-HR or HR newly diagnosed APML, with a median age of 41 years (range 15 to 69). Only those with HR APML are included here. The intervention arm of the nonrandomised non-inferiority trial included people with either standard-risk or HR newly diagnosed APML; only those with HR APML are included here (median age 12.6 years, range 1.1 to 20.8). 2-year event-free survival rate[3] • One subgroup of the intervention arm of an RCT (Wang et al 2022) showed that, following induction and consolidation with ATO+ATRA, the 2year event-free survival rate was 85% (18/21 patients). One subgroup of the intervention arm of a non-randomised non-inferiority trial (Kutny et al 2022) showed that, following induction treatment with ATO+ATRA+idarubicin and consolidation with ATO+ATRA, the 2-year event-free survival rate was 96.4%, (90% CI 88.2% to 98.8%; 54/56 patients). **(VERY LOW)** **Two studies provided very low certainty non-comparative evidence that between 85% and 96.4% of people with HR newly diagnosed APML treated with ATO+ATRA (+idarubicin in one study) during induction and ATO+ATRA during consolidation were still alive at two years follow-up without having experienced an event such as failure to achieve haematologic/molecular remission, relapse or death.**

[3] Kutny et al 2022 describe event-free survival as: “time from study entry until failure to achieve haematologic complete remission or haematologic complete remission with incomplete haematologic recovery by day 70 of induction therapy; time from study entry until failure to achieve molecular remission after consolidation cycle 2, including consolidation therapy, if needed, for those with molecular residual disease; or time from study entry until relapse or death”. Wang et al 2022 define event-free survival as: “time from diagnosis to first event, including death during induction therapy, failure to achieve remission, death during remission, relapse at any site, or the development of second malignant neoplasm.” [4] As reported by Kutny et al 2022: denominator unclear.

Disease-free survival or remission **Certainty of evidence:** Very low	This outcome is important to patients as it means that the signs and symptoms of cancer have reduced, either partially or completely and they are free of all detectable disease. In total, one subgroup of the intervention arm of an RCT, one subgroup of the intervention arm of one non-randomised non-inferiority trial and one retrospective case series provided evidence relating to disease-free survival or remission at either two years or 38 months follow-up. The RCT arm included people with either non-HR or HR newly diagnosed APML, with a median age of 41 years (range 15 to 69). Only those with HR APML are included here. The intervention arm of the nonrandomised non-inferiority trial included people with either standard-risk or HR newly diagnosed APML; only those with HR APML are included here (median age 12.6 years, range 1.1 to 20.8). The retrospective case series included 10 people with HR APL who had survived induction treatment. Only nine of these received ATO and are included here. Cumulative incidence of APML relapse at two years • One subgroup of the intervention arm of one non-randomised noninferiority trial (Kutny et al 2022) showed that, following induction treatment with ATO+ATRA+idarubicin and consolidation with ATO+ATRA, 2/56 (3.9%)[4] patients had APML relapse[4] at up to two years. **(VERY LOW)** 2-year disease-free survival rate

Outcome	**Evidence statement**
	• One subgroup of the intervention arm of an RCT (Wang et al 2022) showed that, following induction and consolidation with ATO+ATRA, the 2year disease-free survival rate[5] was 85% (18/21 patients). **(VERY LOW)** Patients still in remission at median 38 months • One retrospective case series (Shah et al 2020) showed that 100% (9/9) patients with HR APML who survived induction treatment with ATO+ATRA+idarubicin and were treated with ATO+ATRA during consolidation were still in remission at a median of 38 months follow-up (range 14 to 63 months). **(VERY LOW)** **Three studies provided very low certainty non-comparative evidence about the disease-free survival rate. Following induction and consolidation with ATO+ATRA, 85% of patients with HR newly diagnosed APML had survived without relapse at two years. For HR newly diagnosed APML patients treated with ATO+ATRA+idarubicin during induction and ATO+ATRA during consolidation, 3.9% had relapsed within two years. There was very low certainty evidence from one small case series that no patients with HR APML who survived induction with ATO+ATRA+idarubicin and were treated with ATO+ATRA during consolidation had relapsed at a median of 38 months follow-up.**
Important outcomes	

[4] Kutny et al 2022 describe APML relapse as: “time from the end of induction therapy (for patients in haematologic complete remission or haematologic complete remission with incomplete haematologic recovery) to relapse or death, in which deaths without relapse were considered competing events. Disease relapse was defined as the reappearance of promyeloblasts or abnormal promyelocytes (>5%) or 2 consecutive positive results for the presence of PML-RARα on qPCR tests of the bone marrow.”

[5] Wang et al 2022 define disease-free survival as: “time from haematological complete remission (HCR) to either haematological or molecular relapse or death from APL”.

Quality of life **Certainty of evidence:** Not applicable	This is an important outcome for patients as it provides an indication of an individual's general health and self-perceived well-being and their ability to participate in activities of daily living. Validated tools for general quality of life measurements are important patient reported outcome measures to help inform patient-centred decision making and inform health policy. Treatment related impacts on specific quality of life measures are also useful for this purpose. **No evidence was identified for this outcome.**
Hospitalisation **Certainty of evidence:** Very low	This outcome is important to patients as it may represent either disease progression or treatment toxicity. It may have a bearing on the patient's quality of life and inform their treatment decision making. In total, one subgroup of the intervention arm of an RCT provided non-comparative evidence relating to hospitalisation. The RCT arm included people with either nonHR or HR newly diagnosed APML, with a median age of 41 years (range 15 to 69). Only those with HR APML are included here. During induction phase (until HCR[6]) • One subgroup of the intervention arm of an RCT (Wang et al 2022, n=21) showed that the median hospital stay during induction with ATO+ATRA was 29 days (range 16 to 39). **(VERY LOW)** **One study provided very low certainty non-comparative evidence that the median hospital stay during induction with ATO+ATRA for people HR with newly diagnosed APML was 29 days, with a range of 16 to 39 days.**
Activities of daily living **Certainty of evidence:** Not applicable	ADLs are important outcomes to patients as they facilitate enablement and independence, allowing individuals to function in education, work, home, and recreational settings. They encompass patients' individual needs and facilitate inclusion and participation. **No evidence was identified for this outcome.**

Outcome	**Evidence statement**
Safety	

[6] Time to HCR was not specified for HR patients. For the whole intervention arm (n=62), median time to HCR was 32.5 days (14-54 days).

Adverse events **Certainty of evidence:** Very low	These outcomes are important to patients because they will impact on their treatment choices, recovery and could have long term sequelae if they are irreversible. They reflect the tolerability and adverse effects of the treatment. From a service delivery perspective, they reflect the additional demands placed on the health system to manage the adverse consequences of the treatment. In total, one subgroup of the intervention arm of an RCT and one subgroup of the intervention arm of a non-randomised non-inferiority trial provided non-comparative evidence relating to safety during the induction phase, and one non-randomised non-inferiority trial provided non-comparative evidence about safety at a median follow-up of 22.8 months (range 0 to 47.7 months). The RCT arm included people with either non-HR or HR newly diagnosed APML, with a median age of 41 years (range 15 to 69). Only those with HR APML are included here. The induction phase in the RCT lasted until HCR, which was not described for the HR patients specifically[7]. The intervention arm of the non-randomised non-inferiority trial included people with either standard-risk or HR newly diagnosed APML; only those with HR APML are included here (median age 12.6 years, range 1.1 to 20.8). For these patients, induction treatment was from 28 days until a maximum of 70 days. During induction phase[8] • One subgroup of the intervention arm of an RCT (Wang et al 2022) showed that two of 21 patients died during induction treatment with ATO+ATRA. One subgroup of the intervention arm of one non-randomised non-inferiority trial (Kutny et al 2022) showed that none of the 56 patients died during induction treatment with ATO+ATRA+idarubicin. **(VERY LOW)** • One subgroup of the intervention arm of one non-randomised noninferiority trial showed that 17 of 56 (30.4%) patients treated with ATO+ATRA+idarubicin induction therapy had symptoms of differentiation syndrome (Kutny et al 2022). Of these 17/56 patients with symptoms, 64.7% had respiratory distress, 41.2% hypoxia, 58.8% fever, 11.8% erythematous rash, 23.5% pulmonary infiltrates, 17.6% weight gain, 11.8% peripheral oedema, and 11.8% had hypotension. None had pericardial effusion, acute renal failure or congestive heart failure. **(VERY LOW)** • One subgroup of the intervention arm of one non-randomised noninferiority trial (Kutny et al 2022) reported the proportion of patients with ECG QT corrected interval prolonged (by grade). Grade 1 prolonged ECG QT corrected interval was reported for 32.1% of 56 patients, Grade 2 prolonged ECG QT corrected interval for 19.6% and Grade 3 for 7.1%. **(VERY LOW)** • One subgroup of the intervention arm of one non-randomised noninferiority trial (Kutny et al 2022) presented adverse events reported at a frequency of 10% or greater for any treatment cycle (either during induction or during one of the consolidation cycles). During the induction phase.17.9% of 56 patients had no adverse events, 7.1% had ALT increase, 7.1% had AST increase, 58.9% had a prolonged ECG QT corrected interval, 10.7% had decreased fibrogen and 12.5% had hyperglycaemia. **(VERY LOW)** • One subgroup of the intervention arm of an RCT (Wang et al 2022) reported that the median duration of IV antibiotics during induction was 17 days (range 5 to 31 days). **(VERY LOW)** During consolidation phase[9] • One subgroup of the intervention arm of one non-randomised noninferiority trial (Kutny et al 2022) reported the proportion of patients with ECG QT corrected interval prolonged (by grade). During consolidation cycles one to four:

Outcome	Evidence statement

[7] Time to HCR was not specified for HR patients. For the whole intervention arm (n=62), median time to HCR was 32.5 days (14-54 days).
[8] Overall trial median follow-up was 22.8 months (range 0-47.7 months).
[9] Overall trial median follow-up was 22.8 months (range 0-47.7 months).

	○ Grade 1 prolonged ECG QT corrected interval was reported for 47.3% of 56 patients during consolidation cycle 1, 32.7% in cycle 2, 31.5% in cycle 3 and 26.4% during consolidation cycle 4. ○ Grade 2 prolonged ECG QT corrected interval was reported for 5.5% of patients during consolidation cycle 1, 7.3% in cycle 2, 3.7% in cycle 3, and 3.8% during consolidation cycle 4. ○ Grade 3 prolonged ECG QT corrected interval was reported for 1.8% of patients during consolidation cycle 1, not reported in cycle 2, 1.9% in cycle 3, and 1.9% during consolidation cycle 4. **(VERY LOW)** • One subgroup of the intervention arm of one non-randomised noninferiority trial (Kutny et al 2022) presented adverse events reported at a frequency of 10% or greater during each of the four consolidation phases. ○ No adverse events were reported by 40% of 55 patients during consolidation cycle 1, 54.5% of 55 patients in cycle 2, 53.7% of 54 patients in cycle 3 and 62.3% of 53 patients during consolidation cycle 4. ○ An AST increase was reported by 1.8% of patients during consolidation cycle 1 only. ○ Prolonged ECG QT corrected interval was reported by 54.5% during consolidation cycle 1, 40.0% in cycle 2, 37.0% in cycle 3 and 32.1% during cycle 4. **(VERY LOW)** **Two studies provided very low certainty non-comparative evidence about adverse events during the induction phase. Median duration of IV antibiotics during induction with ATO+ATRA was the only adverse event reported separately for the subgroup of patients with HR newly diagnosed APML in one arm of one RCT. Symptoms of differentiation syndrome were experienced during the induction phase (with ATO+ATRA+idarubicin) by 30% of patients in a subgroup of the intervention arm of one non-randomised noninferiority trial. Whilst 18% of patients in that study had no adverse events during induction, 59% of patients had a prolonged ECG QT corrected interval during induction. The study also provided very low certainty noncomparative evidence about adverse events during the consolidation phase. Between 40% and 62% of patients experienced no adverse events across the four consolidation cycles. The proportion of patients with a prolonged ECG QT corrected interval ranged from 32% to 55% across the consolidation cycles.** **None of the studies reported on longer-term adverse effects.**
Abbreviations ALT: alanine amino-transferase; APLM: acute promyelocytic leukaemia; AST: aspartate amino-transferase; ATO: arsenic trioxide; ATRA: all trans retinoic acid; ECG: electrocardiogram; HCR: haematological complete remission; HR: high risk	

In high-risk acute promyelocytic leukaemia what is the cost effectiveness of arsenic trioxide and all trans retinoic acid compared with current standard care?

Outcome	Evidence statement
Cost effectiveness	No evidence was identified for cost effectiveness.

From the evidence selected, are there any subgroups of patients that may benefit from arsenic trioxide and all trans retinoic acid more than the wider population of interest?

Outcome	Evidence statement
Subgroups	No evidence was identified regarding any subgroups of patients that would benefit more from treatment with arsenic trioxide in combination with all trans retinoic acid.

From the evidence selected, what are the criteria used by the research studies to define high-risk acute promyelocytic leukaemia?

Outcome	Evidence statement
Definition of high-risk acute promyelocytic leukaemia	Kutny et al 2022 defined high-risk APML as a WBC count of 10000/μL or higher. Shah et al 2020 assigned patients to risk groups based on laboratory assessment prior to receiving ATRA, but no specific definition of high-risk APML was provided. Diagnosis was confirmed by fluorescence in situ hybridization (FISH) analysis for the promyelocytic leukaemia/retinoic acid receptor alpha (PML/RARA) gene fusion. Wang et al 2022 based risk stratification on WBC count, categorising high-risk APML as a WBC of at least 10×10^9/L.
Abbreviations APML: acute promyelocytic leukaemia; WBC: white blood cell	

From the evidence selected, what are the treatment regimens used to treat highrisk acute promyelocytic leukaemia?

Outcome	Evidence statement
Treatment regimens	Kutny et al 2022 treated patients with ATRA at the first suspicion of APML. Induction therapy included twice daily oral ATRA (12.5mg/m^2 per dose), and daily intravenous ATO (0.15mg/kg) for 28 to 70 days. Patients with high-risk APML also received 4 doses of idarubicin, 12.0mg/m^2 per dose (patients with body surface area <0.6m^2 received 0.4mg/kg per dose) on days 1, 3, 5, and 7 as well as empirical therapy for differentiation syndrome with twice daily dexamethasone, 2.5mg/m^2, on days 1 to 14. All patients received 4 cycles (3 cycles of 8 weeks' duration and 1 cycle of 4 weeks' duration) of ATO/ATRA consolidation therapy and no maintenance therapy. Shah et al 2020 incorporated idarubicin (age adjusted) with ATRA (45mg/m^2/day) + ATO (0.15mg/kg/day) for induction. Consolidation was as per APL0406 regimen.[10] Wang et al 2022 treated high-risk patients with ATRA (40mg/d (BSA < 1.5m^2) or 60 mg/d (BSA ≥ 1.5m^2) (20 to 45mg/m^2/d) in divided doses) and ATO (0.15mg/kg/d) for induction (until HCR), consolidation (until MCR), and maintenance. Both ATO and ATRA were administered for 2 weeks every 4 weeks in the consolidation and maintenance therapy. Synchronous administration of mannitol and ATO was used to prevent central nervous system leukaemia in high-risk patients during consolidation and maintenance phase. Hydroxyurea was given to control the WBC count during the induction phase, at a mean dose of 36.03g (range 19.5 to 59g).
Abbreviations APML: acute promyelocytic leukaemia; ATO: arsenic trioxide; ATRA: all trans retinoic acid; HCR: haematological complete remission; MCR: molecular complete remission	

[10] The reference provided by Shah et al 2020 for the APL0406 regimen describes this as ATRA 45mg/m^2/day for 15 days, starting on weeks 0, 4, 8, 12, 16, 20 and 24 of the consolidation phase, with ATO 0.15mg/kg/day 5 days per week starting on weeks 0, 8, 16 and 24.

6. Discussion

This evidence review considered the clinical effectiveness and safety of arsenic trioxide in combination with all trans retinoic acid (ATRA) compared to chemotherapy in combination with ATRA in patients with newly diagnosed high-risk acute promyelocytic leukaemia (APML). The critical outcomes of interest were overall survival, event-free survival, and disease-free survival or remission. Important outcomes were quality of life, hospitalisation, activities of daily living, and safety. Evidence on cost effectiveness was also sought.

Evidence was available from one subgroup of the intervention arm of an RCT (21/62; Wang et al 2022) (the comparator arm was not in scope for this review), one subgroup of the intervention arm of a non-randomised non-inferiority trial (56/154; Kutny et al 2022) and from 9/10 patients in one retrospective case series (Shah et al 2020). Although the study by Kutny et al 2022 compared outcomes against a historical control group, the control group did not receive ATO during induction and received ATO and chemotherapy during consolidation and maintenance, so could not be included in this review. Therefore, only non-comparative evidence was available for this review.

The RCT and the retrospective case series included mostly adults with high-risk APML (the lower range for age was 15 years in the RCT and 17 years in the case series). The nonrandomised non-inferiority trial included patients aged one to 21 with high-risk APML (upper range 20.8 years). Both trials also included patients with non-high-risk APML in the wider cohort, but only data for those with high-risk APML have been included in this review. The retrospective case series was undertaken at a single centre in the USA and focused solely on people with high-risk APML who had survived induction treatment. The RCT took place at three centres in China, and the non-randomised non-inferiority trial took place at 85 centres in Australia, Canada and the USA. None of the studies were conducted in the UK so their applicability to the patients seen in clinical practice in England is uncertain. Although baseline characteristics of patients were available specifically for high-risk patients in the studies by Kutny et al 2022 and Shah et al 2020, the study by Wang et al 2020 only presented baseline demographic data for the cohort as a whole (by treatment arm), so the characteristics of the high-risk patients could not be ascertained.

Kutny et al 2022 and Shah et al 2020 used ATO+ATRA+idarubicin during induction, and the consolidation treatment was ATO+ATRA. Neither study had a maintenance phase. The RCT by Wang et al 2022 randomised patients to either ATO+ATRA for induction, consolidation and maintenance or ATO+ATRA+chemotherapy for induction, consolidation and maintenance. Only the ATO+ATRA arm is included in this review, as the comparator arm had ATO in addition to ATRA and chemotherapy so was not in scope for this review.

The RCT and non-randomised non-inferiority trial reported outcomes at two years, and the median length of follow-up in the retrospective case series was 38 months (range 14 to 63 months). All three studies reported the critical outcomes overall survival and disease-free survival, with the critical outcome event-free survival also being reported by the non-randomised non-inferiority trial and the RCT. The important outcome safety was reported by both the nonrandomised non-inferiority trial and the RCT. The important outcome hospitalisation was only reported by the RCT. No evidence was available for the important outcomes of quality of life or activities of daily living, and no evidence was identified for cost effectiveness.

The certainty of evidence was very low for all outcomes. The main limitation was the lack of comparative evidence, as one arm from the RCT did not meet the comparator inclusion criteria for this review and the historical controls used by the non-randomised non-inferiority trial had received chemotherapy alongside ATO during consolidation and maintenance phases (and had

not received ATO during induction), so were not in scope for this review. This means that there is no direct evidence to support the comparison of ATO+ATRA versus ATO+chemotherapy that is of interest to this review. The certainty of evidence was downgraded by one level for all outcomes due to the lack of comparative evidence.

Another limitation is the studies' small sample sizes for the patients of relevance to this review. Although part of larger studies, there were only 21 high-risk patients in the in-scope intervention arm of the Wang et al 2022 RCT, and 56 high-risk patients in the relevant arm of the Kutny et al 2022 non-randomised non-inferiority trial. Shah et al 2020 included 10 patients, only nine of whom had received ATO and so were in scope for this review. It should also be noted that this retrospective case series did not specify that the patients should be newly diagnosed. In terms of comparability of the intervention regimen used by the studies, patients in the ATO+ATRA arm of the RCT did not receive idarubicin during induction, whereas those in the non-inferiority trial and the retrospective case series did receive idarubicin alongside ATO+ATRA during induction.

The Wang et al 2022 RCT provided a clear overview of the flow of eligible participants through the trial selection process, but it was not clear whether there was consecutive or complete inclusion of participants in the Kutny et al 2022 study or the retrospective case series by Shah et al 2020. It is therefore possible that some selection bias may have been introduced in the studies by Kutny et al 2022 and Shah et al 2020, so evidence was downgraded by one certainty level for those studies. Of note, patients had to have survived induction to be included in the retrospective case series, so results are only applicable to these patients and survival rates would have been lower if some patients had died during induction. There was no information on the number of patients who died during induction.

Clinical and demographic information was presented for high-risk patients specifically in the studies by Kutny et al 2022 and Shah et al 2020, but Wang et al 2022 only presented this information for each trial arm, which included both people with high-risk (n=21) and non-highrisk (n=41) APML. It is therefore not possible to discern information such as median white blood cell count for high-risk patients specifically in the Wang et al 2022 study (although by the study's definition, these would have had a white blood cell count of at least 10×10^9/L). The extent to which the high-risk patients are characteristic of those in other settings is therefore not clear, so evidence was downgraded by one level.

All three studies reported the critical outcomes of overall survival and disease-free survival, and the larger two studies also reported event-free survival. Although, there was less evidence for the important outcomes. No studies reported quality of life or activities of daily living, and only the RCT reported hospitalisation, as the median duration of hospital stay during induction. In terms of safety, the RCT only reported deaths and use of intravenous antibiotics during the induction phase separately for the high-risk patients; adverse events were only reported by treatment arm, including both non-high-risk and high-risk patients. The non-randomised noninferiority trial reported adverse events during the induction and consolidation treatment phases. The retrospective case series did not report on safety. The studies did not have sufficient followup time to present evidence for the longer-term safety outcomes of interest, such as impact on fertility and cardiotoxicity.

No evidence was identified for the cost effectiveness of ATO+ATRA in patients with newly diagnosed high-risk APML. There was no information in the studies about minimally clinical important differences for any of the outcomes. None of the studies presented evidence for different subgroups, other than stratification by risk group into high-/non-high-risk APML.

7. Conclusion

This review included one subgroup of one arm of an RCT, one subgroup of one arm of a nonrandomised non-inferiority trial and one retrospective case series. In the included studies, patients with high-risk APML received ATO+ATRA during induction (with idarubicin in two studies) and consolidation treatment, and also as maintenance treatment in the RCT. Neither the RCT control arm nor the historical control group for the non-randomised non-inferiority trial had intervention regimens that matched the required comparator for this review, so all trials were treated as case series.

Very low certainty, non-comparative data was available from all three studies for the critical outcomes of overall survival and disease-free survival or remission, and from two studies for the critical outcome of event-free survival. Two-year survival and disease-free survival rates of between 85% and 100% were reported by the studies, with two-year event-free survival rates of between 85% and 96%. Very low certainty, non-comparative evidence was available from one study for the important outcome hospitalisation (only reported for the induction period). None of the studies reported the important outcomes quality of life or activities of daily living. In terms of safety, very low certainty evidence was available from two studies during the induction phase, and from one study during the consolidation phase. During the consolidation cycles (when no chemotherapy was given) between 40% and 62% of patients experienced no adverse events. No evidence was available for longer-term safety.

No evidence on cost effectiveness was identified, and none of the studies provided evidence of any subgroups of people with high-risk APML who may benefit more from ATO+ATRA than the general population of interest.

The main limitation of the evidence was the lack of comparator data. In addition, the studies included small numbers of patients with high-risk APML, which impacts on the precision of their findings. The non-randomised non-inferiority trial and retrospective case series had an unclear risk of selection bias due to a lack of information about consecutive/complete enrolment of eligible patients.

Due to these limitations, it was not possible to draw reliable conclusions about the clinical effectiveness, safety or cost effectiveness of ATO+ATRA compared to ATRA+chemotherapy in people with newly diagnosed high-risk APML.

Appendix A PICO document

The review questions for this evidence review are:

1. In high-risk acute promyelocytic leukaemia what is the clinical effectiveness of arsenic trioxide and all trans retinoic acid compared with current standard care?
2. In high-risk acute promyelocytic leukaemia what is the safety of arsenic trioxide and all trans retinoic acid compared with current standard care?
3. In high-risk acute promyelocytic leukaemia what is the cost effectiveness of arsenic trioxide and all trans retinoic acid compared with current standard care?
4. From the evidence selected, are there any subgroups of patients that may benefit from arsenic trioxide and all trans retinoic acid more than the wider population of interest?

5. From the evidence selected, what are the criteria used by the research studies to define high-risk acute promyelocytic leukaemia?
6. From the evidence selected, what were the treatment regimens used to treat high-risk acute promyelocytic leukaemia?

P –Population and Indication	Patients with newly diagnosed high-risk acute promyelocytic leukaemia (APML/APL). [This may be defined in the literature as a white cell count ≥ 10,000/µl or ≥$10x10^9$/L.] Subgroups of interest: • Age
I – Intervention	Arsenic trioxide in combination with all trans retinoic acid (ATRA). [This can be given in combination with idarubicin chemotherapy during the induction phase only.] [Oral and intravenous routes of administration are of interest] [This may be given alongside best supportive care e.g., hydroxycarbamide, prednisolone/ dexamethasone.]
C – Comparator(s)	Chemotherapy in combination with all trans retinoic Acid (ATRA). [This is usually anthracycline chemotherapy (primarily idarubicin but could also include daunorubicin, etoposide, doxorubicin or mitoxantrone).] [This may be given alongside best supportive care e.g., hydroxycarbamide, prednisolone/ dexamethasone.]
O – Outcomes	**Clinical Effectiveness** Minimally clinically important differences (MCIDs) are not known unless stated. *Critical to decision-making:* • **Overall survival**

	This outcome is important to patients as patients with high-risk APML have a higher mortality rate due to risk of fatal haemorrhage. Improved overall survival is an important marker of effective treatment, although it does not provide information about a patient's health and wellbeing during that time. [Overall survival is conventionally thought of as the gold standard for assessing survival benefit of cancer drug treatments and is usually defined as time from diagnosis to death. Mortality, particularly from CNS haemorrhage, reported in induction therapy is particularly relevant in APML.]

	• **Event-free survival** *This outcome is important to patients because it represents the time during which their disease is not progressing. Stable disease might represent longer survival and disease stability may result in patients experiencing fewer symptoms from the disease itself. It can be determined sooner than overall survival outcome measures.* [Event-free survival is a composite measure and could be defined by the following: disease-free survival; time from diagnosis to first event, including death during induction therapy; failure to achieve remission; relapse at any site; development of second malignant neoplasm; time from haematological complete remission (HCR) to either haematological or molecular relapse or death from APML. Haematological complete relapse or molecular relapse is defined as the reversion to positivity in two consecutive bone marrow samples performed at least two weeks apart.] • **Disease-free survival or remission** *This outcome is important to patients as it means that the signs and symptoms of cancer have reduced, either partially or completely and they are free of all detectable disease.* [Disease-free survival/ remission are binary measures that can be defined as the time from haematological/cytogenic/molecular complete remission (CR) to either haematological/cytogenic/molecular relapse or death from APL. Haematological remission: ○ the bone marrow is regenerating normal hematopoietic cells and contains <5% blast cells by morphology

	○ the absolute neutrophil count in peripheral blood should be>1.0x10^9 /l and the platelet count >100x10^9 /l. Cytogenetic remission: ○ disappearance of the diagnostic clonal abnormality. Molecular remission: ○ absence of PML-RARα fusion transcript in bone marrow by RQ PCR, with an assay sensitivity of at least 10^{-4}] *Important to decision-making:* • **Quality of Life** *This is an important outcome for patients as it provides an indication of an individual's general health and selfperceived well-being and their ability to participate in activities of daily living. Validated tools for general quality of life measurements are important patient reported outcome measures to help inform patientcentred decision making and inform health policy. Treatment related impacts on specific quality of life measures are also useful for this purpose.* [Examples of quality-of-life tools include but are not limited to Paediatric Quality of Life Inventory (PedsQL), the Child Health Questionnaire (CHQ), or the Quality-ofLife Scale for Children (QOL-C), QLQ-OV28, QLQ-C30, QLQ-FA12, EQ-5D and SF-36. Longer term cardiac function might also be reported in terms of quality of life.] • **Hospitalisation** *This outcome is important to patients as it may represent either disease progression or treatment toxicity. It may have a bearing on the patient's quality of life and inform their treatment decision making.* [This may be described as requirement for outpatient or inpatient treatment, number of acute admissions due to APML or treatment complications, length of hospital admissions.] • **Activities of Daily Living** *ADLs are important outcomes to patients as they facilitate enablement and independence, allowing individuals to function in education, work, home, and recreational settings. They encompass patients' individual needs and facilitate inclusion and participation.* [ADLs can be measured using assessments such as: ○ Timed task completion (e.g., timed repeatable test such as dressing, meal preparation or patient specific ADL goal)

	○ ADLs assessment using a tool (e.g., Barthel Index (BI) or Independence in Activities of Daily Living (ADL) ○ Subjective/self-reported assessment (e.g., by the individual, carer, or MDT. This could include selfreported questionnaires such as participation in work, school and other activities).] **Safety** *These outcomes are important to patients because they will impact on their treatment choices, recovery and could have long term sequelae if they are irreversible. They reflect the tolerability and adverse effects of the treatment. From a service delivery perspective, they reflect the additional demands placed on the health system to manage the adverse consequences of the treatment.* [Particular outcomes of interest might include long term effects of treatment such as impact on fertility and cardiotoxicity, need for central line insertion and associated complications.] **Cost effectiveness**
Inclusion criteria	
Study design	Systematic reviews, randomised controlled trials, controlled clinical trials, cohort studies. If no higher-level quality evidence is found, case series can be considered.
Language	English only
Patients	Human studies only
Age	All ages
Date limits	2013-2023
Exclusion criteria	
Publication type	Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials, guidelines and preprints
Study design	Case reports, resource utilisation studies

Appendix B Search strategy

Medline, Embase and the Cochrane Library were searched limiting the search to papers published in English language in the last 10 years. Conference abstracts, commentaries, letters, editorials and case reports were excluded.

Search dates: 1 January 2013 to 14 September 2023

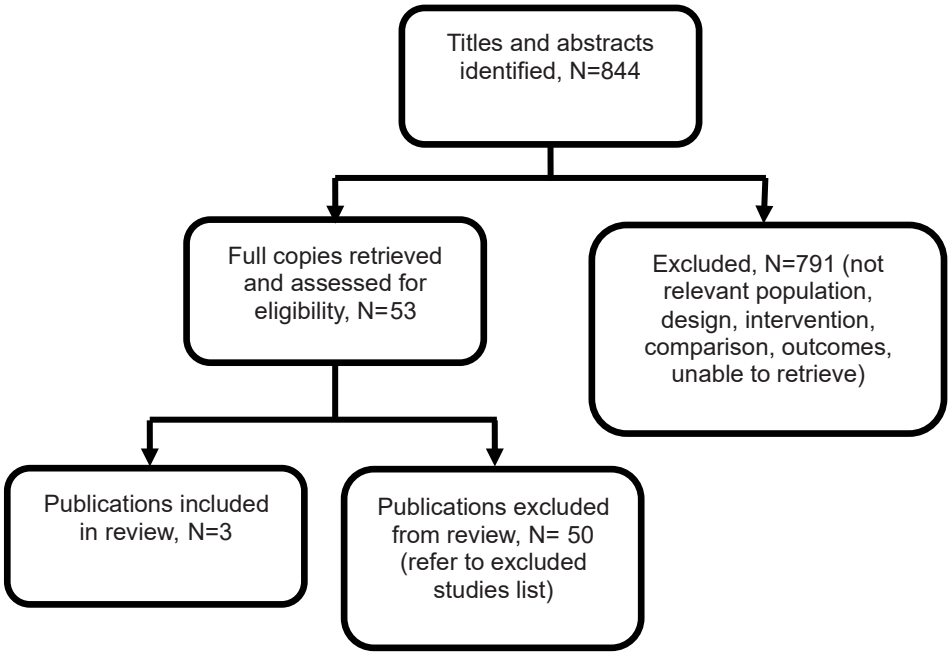
Medline search

1	leukemia, promyelocytic, acute/
2	((acute or high risk or highrisk) and leuk?emi*).ti,kf. and promyelocyt*.ti,ab,kf.
3	promyelocytic leuk?emi*.ti,kf. or ((acute or high risk or highrisk) adj5 promyelocytic leuk?emi*).ab.
4	((apl or apml) and leuk?emi*).ti,ab,kf.
5	1 or 2 or 3 or 4
6	Arsenic Trioxide/
7	((arsenic or diarsenic) adj trioxide).ab. or arsenic.ti,kf.
8	(tetra arsenic adj (oxide or hexaoxide)).ti,ab,kf.
9	(trisenox or trixenox or arsenolite or arsenous anhydride).ti,ab,kf.
10	6 or 7 or 8 or 9
11	5 and 10
12	exp animals/ not humans/
13	11 not 12
14	limit 13 to (english language and yr="2013 -Current")
15	limit 14 to (meta analysis or "systematic review" or "reviews (maximizes specificity)")
16	(comment or editorial or letter or review).pt. or case report.ti.
17	14 not 16
18	15 or 17

Appendix C Evidence selection

The literature searches identified 844 references. These were screened using their titles and abstracts and 53 references were obtained in full text and assessed for relevance. Of these, 3 references are included in the evidence summary. The remaining 50 references were excluded and are listed in Appendix D.

Figure 1- Study selection flow diagram



References submitted with Preliminary Policy Proposal

Reference	Paper selection - decision and rationale if excluded
Kutny MA, Alonzo TA, Abla O, Rajpurkar M, Gerbing RB, Wang YC, et al. Assessment of arsenic trioxide and all-trans retinoic acid for the treatment of pediatric acute promyelocytic leukemia: a report from the Children's Oncology Group AAML1331 Trial. JAMA Oncol. 2022 Jan 1;8(1):79-87	Included.
Wang HY, Gong S, Li GH, Yao YZ, Zheng YS, Lu XH, et al. An effective and chemotherapy-free strategy of alltrans retinoic acid and arsenic trioxide for acute promyelocytic leukemia in all risk groups (APL15 trial). Blood Cancer J. 2022 Nov 21;12(11):158	Included.
Jabbar N, Khayyam N, Arshad U, Maqsood S, Hamid SA, Mansoor N. Outcome analysis of childhood acute promyelocytic leukemia treated with ATRA and arsenic trioxide, and limited dose anthracycline. Indian J Hematol Blood Transfus 37, 569–575 (2021)	Excluded. Intervention out of scope: chemotherapy given post induction (during maintenance phase).

Appendix D Excluded studies table

Study reference	Reason for exclusion
Autore F, Chiusolo P, Sora F, Giammarco S, Laurenti L, Innocenti I, et al. Efficacy and Tolerability of First Line Arsenic Trioxide in Combination With All-Trans Retinoic Acid in Patients With Acute Promyelocytic Leukemia: Real Life Experience. Front. 2021;11:614721.	Results not reported separately for high-risk (HR) patients.
Bankar A, Korula A, Kulkarni UP, Devasia AJ, Na F, Lionel S, et al. Resource utilization and cost effectiveness of treating acute promyelocytic leukaemia using generic arsenic trioxide. Br J Haematol. 2020;189(2):269-78.	Population out of scope: low-intermediate risk.
Burnett AK, Russell NH, Hills RK, Bowen D, Kell J, Knapper S, et al. Arsenic trioxide and all-trans retinoic acid treatment for acute promyelocytic leukaemia in all risk groups (AML17): results of a randomised, controlled, phase 3 trial. Lancet Oncol. 2015;16(13):1295-305.	Intervention out of scope: gemtuzumab ozogamicin added for HR patients.

Chamoun K, Kantarjian HM, Wang X, Naqvi K, Aung F, Garcia-Manero G, et al. Unrecognized fluid overload during induction therapy increases morbidity in patients with acute promyelocytic leukemia. Cancer. 2019;125(18):3219-24.	Intervention out of scope: gemtuzumab ozogamicin added.
Chen J, Chen S, Luo H, Wu W, Wang S. The application of arsenic trioxide in cancer: An umbrella review of meta-analyses based on randomized controlled trials. J Ethnopharmacol. 2023;316:116734.	Results not reported separately for HR patients.
Chen L, Wang J, Hu X, Xu X. Meta-analysis of all-trans retinoic acid-linked arsenic trioxide treatment for acute promyelocytic leukemia. Hematol. 2014;19(4):202-7.	Results not reported separately for HR patients.
Chen X, Hong Y, Zheng P, You X, Feng J, Huang Z, et al. The economic research of arsenic trioxide for the treatment of newly diagnosed acute promyelocytic leukemia in China. Cancer. 2020;126(2):311-21.	Population out of scope: low-intermediate risk.
Cheng Y, Zhang L, Wu J, Lu A, Wang B, Liu G. Long-term prognosis of childhood acute promyelocytic leukaemia with arsenic trioxide administration in induction and consolidation chemotherapy phases: a single-centre experience. Eur J Haematol. 2013;91(6):483-9.	Intervention out of scope: chemotherapy given after induction phase (during consolidation and maintenance phases).
Chien N, Varghese C, Green TN, Chan G, Theakston E, Eaddy N, et al. Treatment outcomes of patients with acute promyelocytic leukaemia between 2000 and 2017, a retrospective, single centre experience. Leuk Res. 2020;93:106358.	Outcomes out of scope for the in-scope patients.
Daver N, Kantarjian H, Marcucci G, Pierce S, Brandt M, Dinardo C, et al. Clinical characteristics and outcomes in patients with acute promyelocytic leukaemia and hyperleucocytosis. Br J Haematol. 2015;168(5):646-53.	Intervention out of scope: gemtuzumab ozocamicin added.
Doria-Rose VP, Harlan LC, Stevens J, Little RF. Treatment of de novo acute myeloid leukemia in the United States: a report from the Patterns of Care program. Leuk Lymphoma. 2014;55(11):2549-55.	Results not reported separately for HR patients.
Efficace F, Cannella L, Breccia M, Olivieri J, Platzbecker U, Vignetti M. Healthrelated quality of life in patients with acute promyelocytic leukemia: a systematic literature review. Expert Rev Hematol. 2021;14(7):645-54.	SR including only one relevant study which does not report results separately for HR patients for outcomes of interest.
Eghtedar A, Rodriguez I, Kantarjian H, O'Brien S, Daver N, Garcia-Manero G, et al. Incidence of secondary neoplasms in patients with acute promyelocytic leukemia treated with all-trans retinoic acid plus chemotherapy or with all-trans retinoic acid plus arsenic trioxide. Leuk Lymphoma. 2015;56(5):1342-5.	Outcomes out of scope.
Ge F, Zhang Y, Cao F, Li J, Hou J, Wang P, et al. Arsenic trioxide-based therapy is suitable for patients with psoriasis-associated acute promyelocytic leukemia - A retrospective clinical study. Hematol. 2016;21(5):287-94.	Intervention out of scope.

Study reference	**Reason for exclusion**
Gill H, Raghupathy R, Lee CYY, Yung Y, Chu HT, Ni MY, et al. Acute promyelocytic leukaemia: population-based study of epidemiology and outcome with ATRA and oral-ATO from 1991 to 2021. BMC Cancer. 2023;23(1):141.	Results for HR patients only presented graphically.
Gill H, Yung Y, Chu HT, Au WY, Yip PK, Lee E, et al. Characteristics and predictors of early hospital deaths in newly diagnosed APL: a 13-year population-wide study. Blood Adv. 2021;5(14):2829-38.	Results not reported separately for HR patients.
Gong S, Wang H, Zhang H, Liu W, Zhang X, Zhao C. Real-world data on the doserelated effect of arsenic trioxide in the relapse of acute promyelocytic leukemia. Mol. 2020;13(6):91.	Intervention out of scope: chemotherapy given post induction, described as ‘post-remission’ with no further details.

Hou J, Wang S, Zhang Y, Fan D, Li H, Yang Y, et al. Causes and prognostic factors for early death in patients with acute promyelocytic leukemia treated with singleagent arsenic trioxide. Ann Hematol. 2017;96(12):2005-13.	Intervention out of scope: no all-trans retinoic acid.
Hu J, Sun Q, Fang W, Wang Q. Effect of combination of all-trans retinoic acid and arsenic trioxide on apoptosis of acute promyelocytic leukemia cells. Cell Mol Biol (Noisy-le-grand). 2019;65(4):97-100.	Paper not available.
Huang J, Sun M, Wang Z, Zhang Q, Lou J, Cai Y, et al. Induction treatments for acute promyelocytic leukemia: a network meta-analysis. Oncotarget. 2016;7(44):71974-86.	Results not reported separately for HR patients.
Jabbar N, Khayyam N, Arshad U, Maqsood S, Hamid SA, Mansoor N. An Outcome Analysis of Childhood Acute Promyelocytic Leukemia Treated with Atra and Arsenic Trioxide, and Limited Dose Anthracycline. Indian J. 2021;37(4):569-75.	Intervention out of scope: chemotherapy given post induction (during maintenance phase).
Javed H, Chudary QU, Iftikhar R, Shahbaz N, Ali M, Hamayun S. Treatment outcomes of patients with newly diagnosed acute promyelocytic leukemia; experience from a developing country. J Ayub Med Coll Abbottabad. 2022;34(4):791-6.	Results not reported separately for in-scope patients.
Kapoor J, Mirgh SP, Agrawal N, Khushoo V, Tejwani N, Singh R, et al. High risk acute promyelocytic leukemia - an enigma for hematologists: optimizing treatment with APML-4 Protocol. Indian J. 2022;38(2):394-402.	Intervention out of scope: chemotherapy given post induction phase (during maintenance phase).
Kayser S, Krzykalla J, Elliott MA, Norsworthy K, Gonzales P, Hills RK, et al. Characteristics and outcome of patients with therapy-related acute promyelocytic leukemia front-line treated with or without arsenic trioxide. Leukemia. 2017;31(11):2347-54.	Results not reported separately for in-scope patients.
Kayser S, Rahme R, Martinez-Cuadron D, Ghiaur G, Thomas X, Sobas M, et al. Outcome of older (>=70 years) APL patients frontline treated with or without arsenic trioxide-an International Collaborative Study. Leukemia. 2020;34(9):2333-41.	Population out of scope: does not include in-scope patients on in-scope intervention.
Kim PG, Bridgham K, Chen EC, Vidula MK, Pozdnyakova O, Brunner AM, et al. Incident adverse events following therapy for acute promyelocytic leukemia. Leuk Res Rep. 2018;9:79-83.	Results not reported separated for in-scope patients.
Kruse M, Wildner R, Barnes G, Martin M, Mueller U, Lo-Coco F, et al. Budgetary impact of treating acute promyelocytic leukemia patients with first-line arsenic trioxide and retinoic acid from an Italian payer perspective. PLoS ONE. 2015;10(8):e0134587.	Population out of scope: low-intermediate risk.
Kutny MA, Geyer S, Laumann KM, Gregory J, Willman CL, Stock W, et al. Outcome for pediatric acute promyelocytic leukemia patients at Children's Oncology Group sites on the Leukemia Intergroup Study CALGB 9710 (Alliance). Pediatr Blood Cancer. 2019;66(3):e27542.	Intervention out of scope: no arsenic trioxide (ATO) in induction phase.

Study reference	**Reason for exclusion**
Lachaine J, Mathurin K, Barakat S, Schuh AC. Economic evaluation of arsenic trioxide for treatment of newly diagnosed acute promyelocytic leukaemia in Canada. Hematol Oncol. 2015;33(4):229-38.	Population out of scope: low-intermediate risk.
Leech M, Morris L, Stewart M, Smith BD, Bashey A, Holland K, et al. Real-life experience of a brief arsenic trioxide-based consolidation chemotherapy in the management of acute promyelocytic leukemia: favorable outcomes with limited anthracycline exposure and shorter consolidation therapy. Clin Lymphoma Myeloma Leuk. 2015;15(5):292-7.	Intervention out of scope: no ATO in induction phase.

Li X, Wang C, Chen G, Ji B, Xu Y. Combined chemotherapy for acute promyelocytic leukemia: a meta-analysis. Hematol. 2017;22(8):450-9.	Results not reported separated for in-scope patients.
Long ZJ, Hu Y, Li XD, He Y, Xiao RZ, Fang ZG, et al. ATO/ATRA/anthracyclinechemotherapy sequential consolidation achieves long-term efficacy in primary acute promyelocytic leukemia. PLoS ONE. 2014;9(8):e104610.	Intervention out of scope: no ATO in induction phase.
Lou Y, Lu Y, Zhu Z, Ma Y, Suo S, Wang Y, et al. Improved long-term survival in all Sanz risk patients of newly diagnosed acute promyelocytic leukemia treated with a combination of retinoic acid and arsenic trioxide-based front-line therapy. Hematol Oncol. 2018;03:03.	Intervention out of scope: chemotherapy post induction phase (during consolidation phase).
Lou Y, Ma Y, Suo S, Ni W, Wang Y, Pan H, et al. Prognostic factors of patients with newly diagnosed acute promyelocytic leukemia treated with arsenic trioxide-based frontline therapy. Leuk Res. 2015;39(9):938-44.	Outcomes out of scope.
Lou Y, Suo S, Tong H, Ye X, Wang Y, Chen Z, et al. Characteristics and prognosis analysis of additional chromosome abnormalities in newly diagnosed acute promyelocytic leukemia treated with arsenic trioxide as the front-line therapy. Leuk Res. 2013;37(11):1451-6.	Intervention out of scope: chemotherapy post induction phase (during consolidation phase).
Luo JS, Zhang XL, Huang DP, Chen YQ, Wan WQ, Mai HR, et al. Differentiation syndrome and coagulation disorder - comparison between treatment with oral and intravenous arsenics in pediatric acute promyelocytic leukemia. Ann Hematol. 2023;102(7):1713-21.	Patients randomised to oral vs intravenous ATO in induction phase only. Comparator out of scope.
Ma Y, Liu L, Jin J, Lou Y. All-trans retinoic acid plus arsenic trioxide versus all-trans retinoic acid plus chemotherapy for newly diagnosed acute promyelocytic leukemia: a meta-analysis. PLoS ONE. 2016;11(7):e0158760.	Systematic review and meta-analysis which only includes 1 relevant study (Burnett 2015), assessed separately.
Min GJ, Cho BS, Park SS, Park S, Jeon YW, Yahng SA, et al. Safety and efficacy of arsenic trioxide and all-trans retinoic acid therapy in acute promyelocytic leukemia patients with a high risk for early death. Ann Hematol. 2020;99(5):973-82.	Majority of patients out of scope. Larger case series with all patients in scope available.
Rodriguez-Rodriguez S, Guerrero-Torres L, Diaz-Huizar MJ, Pomerantz A, OrtizVilchis MDP, Demichelis-Gomez R. Cost-effectiveness of the regimen proposed by the International Consortium on Acute Promyelocytic Leukemia for the treatment of newly diagnosed patients with Acute Promyelocytic Leukemia. Hematol. 2021;43(4):476-81.	Intervention out of scope: chemotherapy given post induction (during consolidation and maintenance phases).
Singh C, Yanamandra U, Karunakaran P, Jindal N, Kumar SR, Saini N, et al. Longterm real-world outcomes of patients with acute promyelocytic leukaemia treated with arsenic trioxide and all-trans retinoic acid without chemotherapy-a retrospective, single-centre study. Br J Haematol. 2023;201(2):249-55.	Intervention out of scope: chemotherapy post induction phase (during maintenance phase).
Steffenello-Durigon G, Bigolin A, Moraes ACR, Rudolf-Oliveira RC, Moral J, SantosSilva MC. Follow-up and outcome of the twelve-year experience in adult patients with acute promyelocytic leukemia. Hematol. 2021;43(1):21-7.	Population out of scope. Only 6 (13.6%) of whole cohort had ATO, and only 11 (25%) of whole cohort were HR. No information
Study reference	**Reason for exclusion**
	on whether HR patients had ATO.
Tao S, Wang C, Chen Y, Deng Y, Song L, Shi Y, et al. Long-term effect of all-trans retinoic acid and arsenic trioxide sequential maintenance in patients with acute promyelocytic leukemia. Leuk Lymphoma. 2019;60(3):711-9.	Results not reported separated for in-scope patients.

Wu F, Wu D, Ren Y, Duan C, Chen S, Xu A. Bayesian network meta-analysis comparing five contemporary treatment strategies for newly diagnosed acute promyelocytic leukaemia. Oncotarget. 2016;7(30):47319-31.	Systematic review and meta-analysis which only includes 1 relevant study (Burnett 2015), assessed separately.
Wu Y, Ke P, Zhou H, Wu D, Chen S, Qiu H, et al. Safety and efficacy of different doses of anthracyclines combined with arsenic trioxide and all-trans retinoic acid in the treatment of de novo acute promyelocytic leukemia. Hematol. 2021;26(1):271-6.	Results not reported separated for in-scope HR patients.
Zhang L, Zhang Y, Li Z. Therapeutic effects of arsenic trioxide plus all-trans retinoic acid on acute promyelocytic leukemia. International Journal of Clinical and Experimental Medicine. 2019;12(6):7536-44.	Intervention out of scope: chemotherapy post induction phase (during consolidation and maintenance phases).
Zhang Y, Wang L, Zhang R, Qi P, Xie J, Shi H, et al. Long-term follow-up of children with acute promyelocytic leukemia treated with Beijing Children's Hospital APL 2005 protocol (BCH-APL 2005). Pediatr Hematol Oncol. 2019;36(7):399-409.	Intervention out of scope: chemotherapy post induction phase (during consolidation and maintenance phases).
Zhang ZX, Lu AD, Wu J, Zuo YX, Jia YP, Zhang LP, et al. Retrospective analysis of data from 73 patients with childhood acute promyelocytic leukaemia receiving modified chemotherapy: a single-centre study. J Cancer Res Clin Oncol. 2021;147(4):1189-201.	Intervention out of scope: chemotherapy post induction phase (during consolidation phase).
Zheng H, Jiang H, Hu S, Liao N, Shen D, Tian X, et al. Arsenic combined with alltrans retinoic acid for pediatric acute promyelocytic leukemia: report from the CCLGAPL2016 Protocol Study. J Clin Oncol. 2021;39(28):3161-70.	Intervention out of scope: chemotherapy post induction phase (during consolidation phase).
Zhu HH, Guo ZP, Jia JS, Jiang Q, Jiang H, Huang XJ. The impact of oral arsenic and all-trans-retinoic acid on coagulopathy in acute promyelocytic leukemia. Leuk Res. 2018;65:14-9.	Results not reported separated for in-scope patients.
Zhu HH, Ma YF, Yu K, Ouyang GF, Luo WD, Pei RZ, et al. Early death and survival of patients with acute promyelocytic leukemia in ATRA plus arsenic era: a population-based study. Front. 2021;11:762653.	Intervention out of scope: chemotherapy post induction phase (during consolidation phase).

Appendix E Evidence table

For abbreviations see list after table

Study details	Population	Interventions	Study outcomes	Appraisal and funding
Kutny MA, Alonzo TA, Abla O, Rajpurkar M, Gerbing RB, Wang YC, et al. Assessment of arsenic trioxide and all-trans retinoic acid for the treatment of pediatric acute promyelocytic leukemia: a report from the Children's Oncology Group AAML1331 Trial. JAMA Oncol. 2022 Jan 1;8(1):79-87 **Study location** 85 centres in Australia, Canada and the USA **Study type** Non-randomised, non-inferiority trial with historical controls (controls not in scope)	**Inclusion criteria** Age 1 to 21 years with newly diagnosed APML. Patients were permitted to have received up to 5 days of ATRA treatment before trial commenced. **Exclusion criteria** Secondary APL, isolated myeloid sarcoma, EKG abnormalities, renal dysfunction, prior chemotherapy **Total sample size** N=56 HR patients (N=154 patients overall, 98 were standard-risk patients) **Baseline characteristics**[11] • 25 (44.6%) female	**Interventions** Induction: ATO+ATRA+idarubicin • Twice daily oral ATRA 12.5mg/m^2 per dose, and daily intravenous ATO, 0.15mg/kg; for at least 28 days until confirmation of haematologic complete remission or haematologic complete remission with incomplete haematologic recovery (maximum 70 days allowed) • 4 doses of idarubicin, 12.0mg/m^2 per dose (patients with	**Critical outcomes** **Overall survival** 2-year OS rate: 56/56 (100%) (90% CI 93.0 to 100) **Event-free survival**[12] 2-year EFS rate: 54/56 (96.4%) (90% CI 88.2 to 98.8) **Disease-free survival or remission** APML relapse[13]: cumulative incidence at 2-years: 2 (3.9%)[14] **Important outcomes**[15] **Safety** Median follow-up: 22.8 months (range 0 to 47.7 months) Early death (during induction): 0/56	This study was appraised using the JBI checklist for case series. 1. Yes 2. Yes 3. Yes 4. Unclear 5. Unclear 6. Yes 7. Yes 8. Yes 9. No 10. Yes **Other comments:** Included as a non-comparative study: although the paper used historical controls from the AAML0631 study, these could not be included here as controls because the participants did not receive ATO during induction and received ATO with chemotherapy during the consolidation and maintenance phase (therefore out of scope).

[11] Baseline characteristics were reported separately for HR patients.
[12] Kutny et al 2022 describe EFS as: “time from study entry until failure to achieve haematologic complete remission or haematologic complete remission with incomplete haematologic recovery by day 70 of induction therapy; time from study entry until failure to achieve molecular remission after consolidation cycle 2, including consolidation therapy, if needed, for those with molecular residual disease; or time from study entry until relapse or death”.
[13] Kutny et al 2022 describe APML relapse as: “time from the end of induction therapy (for patients in haematologic complete remission or haematologic complete remission with incomplete haematologic recovery) to relapse or death, in which deaths without relapse were considered competing events. Disease relapse was defined as the reappearance of promyeloblasts or abnormal promyelocytes (>5%) or 2 consecutive positive results for the presence of PML-RARα on qPCR tests of the bone marrow.”
[14] 3.9% is the value reported by Kutny 2022 for relapse of 2 high-risk patients, denominator unclear.
[15] Hospitalisation only reported for whole cohort, not separately for high-risk patients.

Study details	**Population**	**Interventions**	**Study outcomes**	Appraisal and funding

<table>
<tr>
<td>Children’s Oncology Group AAML1331 study.

Study aim

To examine whether 2-year EFS among paediatric patients with SR and HR APML was non-inferior compared with the 2-year EFS of patients in the AAML0631 study, which was used as the historical control.
Study dates

June 2015 to May 2019</td>
<td>• median age 12.6 years (range 1.1 to 20.8)
• median WBC x1000/μL: 41.1 (range 10.2 to 255.1)

Subgroups

Main analysis stratified into HR and SR</td>
<td>body surface area <0.6m^2 received 0.4mg/kg per dose) on days 1, 3, 5, and 7
• Empirical therapy for differentiation syndrome (twice daily dexamethasone, 2.5 mg/m^2 on days 1 to 14

Consolidation: ATO+ATRA intermittently during 4 cycles (3 8-week cycles and 1 4-week cycle)
Maintenance: none

Duration of therapy: approximately 9 months

Comparators

None (historical controls not in scope as they did not receive ATO during induction and received chemotherapy beyond induction)</td>
<td>Symptoms of differentiation syndrome during induction therapy: 17/56 (30.4%).
These included:
• respiratory distress (11/17, 64.7%)
• hypoxaemia (7/17, 41.2%)
• fever (10/17, 58.8%)
• erythematous rash (2/17, 11.8%)
• pulmonary infiltrates (4/17, 23.5%)
• weight gain (3/17, 17.6%
• peripheral oedema (2/17, 11.8%)
• hypotension (2/17, 11.8%).
• none had pericardial effusion, acute renal failure or congestive heart failure

ECG QT corrected interval prolonged by grade[16]

Grade 1
<table><tr><th>Phase</th><th>Total N</th><th>% with prolonged interval</th></tr><tr><td>Induction</td><td>56</td><td>32.1</td></tr><tr><td>Consol. 1</td><td>55</td><td>47.3</td></tr><tr><td>Consol. 2</td><td>55</td><td>32.7</td></tr><tr><td>Consol. 3</td><td>54</td><td>31.5</td></tr><tr><td>Consol. 4</td><td>53</td><td>26.4</td></tr></table></td>
<td>Baseline characteristics and outcome data were available separately for the subgroup of HR patients in the intervention arm.

‘Unclear’ assessment for items 4 and 5 (complete/consecutive inclusion of participants) as there was no information on inclusion assessment and enrolment, and it was not clear how many eligible patients were not included. ’No’ for item 9 as the paper did not report on the centres’ demographic information.

Source of funding:

Supported by grants from the National Institutes of Health (Children’s Oncology Group) and the St. Baldrick’s Foundation (Children’s Oncology Group).</td>
</tr>
</table>

[16] ECG QT corrected interval prolonged is the only AE reported by grade.

Study details	**Population**	**Interventions**	**Study outcomes**	Appraisal and funding

Grade 2

Phase	Total N	% with prolonged interval
Induction	56	19.6
Consol. 1	55	5.5
Consol. 2	55	7.3
Consol.3	54	3.7%
Consol.4	53	3.8%

Grade 3

Phase	Total N	% with prolonged interval
Induction	56	7.1
Consol.1	55	1.8
Consol.2	55	-
Consol.3	54	1.9
Consol.4	53	1.9

AE reported at a frequency of 10% or greater for any treatment cycle[17]

No adverse events

Phase	Total N	% with AE
Induction	56	17.9
Consol. 1	55	40%
Consol. 2	55	54.5
Consol. 3	54	53.7

[17] This includes AE reported by >10% of patients during induction, so some of the consolidation phase incidences are less than 10%.

			Consol. 4 | 53 | 62.3	

Study details	Population	Interventions	Study outcomes	Appraisal and funding

ALT increase

Phase	Total N	% with AE
Induction	56	7.1

AST increase

Phase	Total N	% with AE
Induction	56	7.1
Consol. 1	55	1.8

ECG QT corrected interval prolonged (all grades)

Phase	Total N	% with AE
Induction	56	58.9
Consol. 1	55	54.5
Consol. 2	55	40.0
Consol. 3	54	37.0
Consol. 4	53	32.1

Fibrogen decreased

Phase	Total N	% with AE
Induction	56	10.7

Hyperglycaemia

Phase	Total N	% with AE
Induction	56	12.5

Shah G, Mikhail FM, Bachiasvili K, Vachhani P, Erba HP, Papadantonakis N. Outcomes of high-risk	**Inclusion criteria** HR APML patients who survived induction and subsequently received consolidation with ATO and	**Interventions** Induction with idarubicin (age adjusted) and ATO+ATRA[18]	**Critical outcomes** Median follow-up: 38 months (range 14 to 63) from diagnosis **Overall survival**	This study was appraised using the JBI checklist for case series. 1. Yes 2. Yes 3. Yes

Study details	**Population**	**Interventions**	**Study outcomes**	Appraisal and funding

[18] One patient in Shah et al 2020 did not receive ATO during induction and one patient did not receive idarubicin.

acute promyelocytic leukemia patients treated with arsenic trioxide (ATO)/all trans retinoic acid (ATRA) based induction and consolidation without maintenance phase: A case Series. Hematol Oncol Stem Cell Ther. 2020;13(3):143-6. **Study location** USA, single centre **Study type** Retrospective case series **Study aim** To report the authors' experience using consolidation with ATRA/ATO without maintenance **Study dates** Retrospective review of patients who were diagnosed with APML between 2013 and 2017	ATRA as per APL0406 trial regimen without maintenance phase. **Exclusion criteria** Not reported **Total sample size** N=10 HR, n=9 received ATO **Baseline characteristics (at diagnosis)[19]** • Median (range) age: • 44.5 (17 to 77) years • 6/10 (60%) female • Median (range) WBC count (x 10^3 /$mm^{3)}$: 42.3 (14.7 to 167.5)	Consolidation with ATO and ATRA as per APL0406 regimen[20] No maintenance phase **Comparators** None	9/9[21] (100%) **Disease-free survival or remission** 0/9 patients relapsed[22]	4. Unclear 5. Unclear 6. Yes 7. Yes 8. Yes 9. Yes 10. Yes **Other comments:** 'Unclear' assessment for items 4 and 5 (complete/consecutive inclusion of participants) as there was no information on this and it was not clear whether other eligible patients were not included. The study included one out of scope patient but was included in the review as the majority of patients were in scope and results could be inferred for inscope patients as all patients survived and none relapsed. Patients had to have survived induction to be included in this retrospective case series, so results are only applicable to these patients and survival rates would have been lower if some patients had died during induction. There was no information on the number of

[19] Baseline characteristics are for the whole case series of 10 patients, not just the 9 in-scope patients.
[20] The reference provided by Shah et al 2020 for the APL0406 regimen describes this as ATRA 45mg/m^2/day for 15 days, starting on weeks 0, 4, 8, 12, 16, 20 and 24 of the consolidation phase, with ATO 0.15mg/kg/day 5 days per week starting on weeks 0, 8, 16 and 24.
[21] Of the whole cohort, 10/10 survived and 0/10 relapsed; only the 9 in-scope patients are reported here.
[22] This outcome was reported as the number of patients who relapsed; disease-free survival or remission was not defined.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
				patients who died during induction. **Source of funding:** Not stated
Wang HY, Gong S, Li GH, Yao YZ, Zheng YS, Lu XH, et al. An effective and chemotherapy-free strategy of all-trans retinoic acid and arsenic trioxide for acute promyelocytic leukemia in all risk groups (APL15 trial). Blood Cancer J. 2022 Nov 21;12(11):158 **Study location** China (3 centres) **Study type** Multicentre RCT: intervention arm only **Study aim** To compare the efficacy of ATRA-ATO versus ATRA-	**Inclusion criteria** Age 15 to 80 years old with newly diagnosed low-risk or HR APML and serum total bilirubin concentration of up to three times the maximum institutional ULN and a serum creatinine concentration of up to 2.5 times the maximum ULN. **Exclusion criteria** Pregnancy, lactation, concomitant severe psychiatric disorder, significant arrhythmias, and other active malignancies. **Total sample size** N=21 HR patients of total n=62 in ATO+ATRA group (33.9%)	**Interventions** ATO+ATRA for induction (until HCR), consolidation (until MCR), and maintenance[23] ATRA: 40mg/d (BSA < 1.5 m^2) or 60mg/d (BSA ≥ 1.5m^2) (20 to 45mg/m^2/d) in divided doses ATO: 0.15 mg/kg/d[24]. Both ATO and ATRA were administered for 2 weeks every 4 weeks in the consolidation and maintenance therapy. Synchronous administration of mannitol and ATO was used to prevent central nervous system leukaemia in HR patients during	**Critical outcomes** **Overall survival** 2-year overall survival: 18[25]/21 (85%) **Event-free survival[26]** 2-year event-free survival: 18/21 (85%) **Disease-free survival[29] or remission** 2-year disease-free survival: 18/19 (94%) **Hospitalisation**	This study was appraised using the JBI checklist for case series[29]. 1. Yes 2. Yes 3. Yes 4. Yes 5. Yes 6. No 7. No 8. Yes 9. Yes 10. Yes **Other comments:** The intervention arm from this RCT is included as a noncomparative case series in this review (comparator not in scope as they received ATO

[23] Route of administration not described by Wang et al 2022.
[24] One person in Wang et al 2022 received ATRA plus Realgar-Indigo naturalis formula (RIF) due to patient choice.
[25] In addition to 2 deaths in the Wang et al 2022 study, 1 person did not receive any post-remission therapy and disease monitoring.
[26] Wang et al 2022 define event-free survival as: "time from diagnosis to first event, including death during induction therapy, failure to achieve remission, death during remission, relapse at any site, or the development of second malignant neoplasm." [29] Wang et al 2022 define disease-free survival as: "time from haematological complete remission (HCR) to either haematological or molecular relapse or death from APL".
[29] Although Wang et al 2022 was an RCT, only the intervention arm could be included so it has been appraised as a noncomparative case series.

			Hospital stay during induction[27], median days (range): 29 (16 to 39) **Safety[28]** • IV antibiotics during induction,	alongside chemotherapy and ATRA during

Study details	**Population**	**Interventions**	**Study outcomes**	Appraisal and funding

[27] Wang et al 2022 stated that induction lasted until HCR. Time to HCR was not specified for HR patients. For the whole intervention arm (n=62), median time to HCR was 32.5 days (14-54 days).
[28] Wang et al 2022 only reported IV antibiotic use during induction and deaths during induction separately for HR patients. Other AEs were only presented for the whole intervention arm, not separately for high-risk patients, so have not been included here. Induction phase lasted until HCR.

ATO plus chemotherapy in people with newly diagnosed APML, to explore the necessity of chemotherapy, especially for HR patients. **Study dates** July 2015 to January 2021	(RCT enrolled 128 HR and non-HR APML patients to ATO+CT+ATRA group (n=66) or ATO+ATRA group (n=62)) **Baseline characteristics (n=62)[30]** • Median age 41 years (range 15 to 69) • 30 (48.4%) female	consolidation and maintenance phase **Comparators** None. RCT comparator arm was ATO+CT+ATRA, so not in scope	median days (range): 17 (5 to 31) • Deaths: 2/21, due to intracranial haemorrhage during induction therapy	consolidation). Only a subgroup of the intervention group were in scope and only results available for this subgroup have been included here. Baseline characteristics were not available for the in-scope patients separately. Items 6 and 7 are marked as 'No' because, although characteristics are clearly reported for each trial arm, no separate demographic/clinical information is available for the in-scope HR patients. **Source of funding:** Grants from The Clinical Research Award Fund of The First Affiliated Hospital of Xi'an Jiaotong University and the Natural Science Foundation of Shaanxi Province.

Abbreviations

AE: adverse event; ALT: alanine amino-transferase; APML: acute promyelocytic leukaemia; AST: aspartate amino-transferase; ATO: arsenic trioxide; ATRA: all trans retinoic acid; BSA: body surface area; CT: chemotherapy; CI: confidence interval; ECG/EKG: electrocardiogram; EFS: event-free survival; HCR: haematological complete remission; HR: high risk; MCR: molecular complete remission; OS: overall survival; RCT: randomised controlled trial; SR: standard risk; ULN: upper limit of normal; WBC: white blood cell

[30] Wang et al 2022 only give baseline characteristics by treatment arm (n=62), not separately for high-risk patients (n=21).

Appendix F Quality appraisal checklists

JBI Critical Appraisal Checklist for Case Series

1. Were there clear criteria for inclusion in the case series?
2. Was the condition measured in a standard, reliable way for all participants included in the case series
3. Were valid methods used for the identification of the condition for all participants included in the case series?
4. Did the case series have consecutive inclusion of participants?
5. Did the case series have complete inclusion of participants?
6. Was there clear reporting of the demographics of the participants in the study?
7. Was there clear reporting of clinical information of the participants?
8. Were the outcomes or follow up results of cases clearly reported?
9. Was there clear reporting of the presenting site(s)/clinic(s) demographic information?
10. Was statistical analysis appropriate?

Appendix G GRADE profiles

Outcome measure, units and timepoint in study (for continuous outcomes indicate if benefit is indicated by higher or lower result)									
QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	ATO+ATRA	CT+ATRA	Result		
Overall survival (1 subgroup of 1 arm of an RCT, 1 subgroup of 1 arm of a non-randomised non-inferiority trial and 1 case series)									
2-year overall survival rate									
1 subgroup of 1 arm of a nonrandomised non-inferiority trial[A] Kutny et al 2022	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	56	None	56/56 (100%) (90% CI 93.0 to 100)	Critical	Very low
1 subgroup of 1 arm of an RCT[B] Wang et al 2022	Serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	21	None	18/21 (85%)[C]	Critical	Very low
Overall survival rate at 38 months median follow-up (range 14 to 63 months)									
1 retrospective case series Shah et al 2020	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	9[D]	None	9/9 (100%)	Critical	Very low
Event-free survival (1 subgroup of 1 arm of an RCT and 1 subgroup of 1 arm of a non-randomised non-inferiority trial)									
2-year event-free survival rate[E]									
1 subgroup of 1 arm of a nonrandomised non-inferiority trial Kutny et al 2022	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	56	None	54/56 (96.4%) (90% CI 88.2 to 98.8)	Critical	Very low
1 subgroup of 1 arm of an RCT Wang et al 2022	Serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	21	None	18/21 (85%)	Critical	Very low

Outcome measure, units and timepoint in study (for continuous outcomes indicate if benefit is indicated by higher or lower result)									
QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	ATO+ATRA	CT+ATRA	Result		
Disease-free survival or remission (1 subgroup of 1 arm of an RCT, 1 subgroup of 1 arm of a non-randomised non-inferiority trial and 1 case series)									
APML relapse[F]: cumulative incidence at 2 years									
1 subgroup of 1 arm of a nonrandomised non-inferiority trial Kutny et al 2022	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	56	None	2/56 (3.9%)[G]	Critical	Very low
2-year disease-free survival[H]									
1 subgroup of 1 arm of an RCT Wang et al 2022	Serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	21	None	18/21 (85%)[C]	Critical	Very low
Patients still in remission at 38 months median follow-up (range 14 to 63 months)									
1 retrospective case series Shah et al 2020	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	9	None	9/9 (100%)	Critical	Very low
Hospitalisation (1 subgroup of 1 arm of an RCT)									
Hospital stay during induction phase[I], median days (range)									
1 subgroup of 1 arm of an RCT Wang et al 2022	Serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	21	None	29 (16 to 39)	Important	Very low
Safety (1 subgroup of 1 arm of an RCT and 1 subgroup of 1 arm of a non-randomised non-inferiority trial)									

Early death during induction phase[l]									
1 subgroup of 1 arm of a nonrandomised non-inferiority trial Kutny et al 2022	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable[4]	56	None	0/56	Important	Very low
1 subgroup of 1 arm of an RCT Wang et al 2022	Serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	21	None	2/21	Important	Very low

Outcome measure, units and timepoint in study (for continuous outcomes indicate if benefit is indicated by higher or lower result)									
QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	ATO+ATRA	CT+ATRA	Result		
Symptoms of differentiation syndrome during induction phase (range 28 to 70 days)									
1 subgroup of 1 arm of a nonrandomised non-inferiority trial Kutny et al 2022	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	56	None	Patients with symptoms of differentiation syndrome: 17/56 (30.4%). Symptoms included: • respiratory distress (11/17, 64.7%) • hypoxemia (7/17, 41.2% • fever (10/17, 58.8%) • erythematous rash (2/17) 11.8%) • pulmonary infiltrates , (4/17, 23.5%) • weight gain (3/17, 17.6% • peripheral oedema (2/1 11.8%) • hypotension (2/17, 11.8%). • None had pericardial effusion, acute renal failure or congestive he failure. rt	Important	Very low

ECG QT corrected interval prolonged by grade at 22.8 months median follow-up (range 0 to 47.7 months)									
1 subgroup of 1 arm of a nonrandomised non-inferiority trial Kutny et al 2022	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	56	None	ECG QT corrected interval prolonged Grade 1 Phase / Total N / % with prolonged interval Induction 56 32.1 Consol. 1 55 47.3 Consol. 2 55 32.7 Consol. 3 54 31.5 Consol. 4 53 26.4	Important	Very low

Outcome measure, units and timepoint in study (for continuous outcomes indicate if benefit is indicated by higher or lower result)					
QUALITY	**Summary of findings**		**IMPORTANCE**	**CERTAINTY**	
	No of patients	**Effect**			

<table>
<tr><th>Study</th><th>Risk of bias</th><th>Indirectness</th><th>Inconsistency</th><th>Imprecision</th><th>ATO+ATRA</th><th>CT+ATRA</th><th>Result</th><th></th><th></th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>Grade 2
<table><tr><th>Phase</th><th>Total N</th><th>% with prolonged interval</th></tr><tr><td>Induction</td><td>56</td><td>19.6</td></tr><tr><td>Consol. 1</td><td>55</td><td>5.5</td></tr><tr><td>Consol. 2</td><td>55</td><td>7.3</td></tr><tr><td>Consol.3</td><td>54</td><td>3.7%</td></tr><tr><td>Consol.4</td><td>53</td><td>3.8%</td></tr></table>Grade 3
<table><tr><th>Phase</th><th>Total N</th><th>% with prolonged interval</th></tr><tr><td>Induction</td><td>56</td><td>7.1</td></tr><tr><td>Consol.1</td><td>55</td><td>1.8</td></tr><tr><td>Consol.2</td><td>55</td><td>-</td></tr><tr><td>Consol.3</td><td>54</td><td>1.9</td></tr><tr><td>Consol.4</td><td>53</td><td>1.9</td></tr></table></td><td></td><td></td></tr>
<tr><td colspan="10">Adverse event reported at a frequency of 10% or greater for any treatment cycle at 22.8 months median follow-up (range 0 to 47.7 months)</td></tr>
<tr><td>1 subgroup of 1 arm of a nonrandomised non-inferiority trial

Kutny et al 2022</td><td>Serious limitations[1]</td><td>Serious indirectness[2]</td><td>Not applicable</td><td>Not calculable</td><td>56</td><td>None</td><td>No adverse events<table><tr><th>Phase</th><th>Total N</th><th>% with AE</th></tr><tr><td>Induction</td><td>56</td><td>17.9</td></tr><tr><td>Consol. 1</td><td>55</td><td>40</td></tr><tr><td>Consol. 2</td><td>55</td><td>54.5</td></tr><tr><td>Consol. 3</td><td>54</td><td>53.7</td></tr><tr><td>Consol. 4</td><td>53</td><td>62.3</td></tr></table></td><td>Important</td><td>Very low</td></tr>
</table>

Outcome measure, units and timepoint in study (for continuous outcomes indicate if benefit is indicated by higher or lower result)									
QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	ATO+ATRA	CT+ATRA	Result		
							ALT increase Phase / Total N / % with AE Induction / 56 / 7.1 AST increase Phase / Total N / % with AE Induction / 56 / 7.1 Consol. 1 / 55 / 1.8 ECG QT corrected interval prolonged Phase / Total N / % with AE Induction / 56 / 58.9 Consol. 1 / 55 / 54.5 Consol. 2 / 55 / 40.0 Consol. 3 / 54 / 37.0 Consol. 4 / 53 / 32.1 Fibrogen decreased Phase / Total N / % with AE Induction		

							56 | 10.7 Hyperglycamia Phase | Total N | % with AE Induction | 56 | 12.5		
IV antibiotics during induction phase[I], median days (range) (benefit indicated by shorter duration)									
1 subgroup of 1 arm of an RCT Wang et al 2022	Serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	21	None	17 (5 to 31)	Important	Very low
Outcome measure, units and timepoint in study (for continuous outcomes indicate if benefit is indicated by higher or lower result)									
QUALITY					**Summary of findings**			**IMPORTANCE**	**CERTAINTY**
					No of patients		**Effect**		
Study	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**ATO+ATRA**	**CT+ATRA**	**Result**		

Abbreviations
AE: adverse event; ALT: alanine amino-transferase; AST: aspartate amino-transferase; ATO: arsenic trioxide; ATRA: all trans retinoic acid; CT: chemotherapy; CI: confidence interval; ECG: electrocardiogram; HCR: haematological complete remission; IV: intravenous; RCT: randomised controlled trial

1 Risk of bias: serious limitations due to unclear reporting of inclusion assessment and enrolment of participants (in relation to non-consecutive and/or incomplete inclusion) and reporting of the centres' demographic information.
2 Indirectness: serious indirectness due to no comparison across treatment arms.
3 Risk of bias: serious limitations due to unclear reporting of study participants (baseline data not presented separately for in-scope patients). 4 Imprecision not calculable despite having 0 events as this study is being appraised as a case series.

A Only a subgroup of the intervention arm of the non-randomised non-inferiority arm could be included. It has therefore been appraised as a case series with an initial 'low' certainty evidence grade.
B Although Wang et al 2022 was an RCT, only a subgroup of the intervention arm could be included. It has therefore been appraised as a case series with an initial 'low' certainty evidence grade.
C In addition to 2 deaths in the Wang et al 2022 study, 1 person did not receive any post-remission therapy and disease monitoring. D Although there were 10 patients in the Shah et al 2020 study, only 9 received ATO.
E Kutny et al 2022 describe EFS as: "time from study entry until failure to achieve haematologic complete remission or haematologic complete remission with incomplete haematologic recovery by day 70 of induction therapy; time from study entry until failure to achieve molecular remission after consolidation cycle 2, including consolidation therapy, if needed, for those with molecular residual disease; or time from study entry until relapse or death". Wang et al 2022 define event-free survival as: "time from diagnosis to first event, including death during induction therapy, failure to achieve remission, death during remission, relapse at any site, or the development of second malignant neoplasm."
F Kutny et al 2022 describe APML relapse as: "time from the end of induction therapy (for patients in hematologic complete remission or haematologic complete remission with incomplete haematologic recovery) to relapse or death, in which deaths without relapse were considered competing events. Disease relapse was defined as the reappearance of promyeloblasts or abnormal promyelocytes (>5%) or 2 consecutive positive results for the presence of PML-RARα on qPCR tests of the bone marrow." G As reported by Kutny et al 2022: denominator unclear.

H Wang et al 2022 define disease-free survival as: “time from haematological complete remission (HCR) to either haematological or molecular relapse or death from APL”.

I Wang et al 2022 stated that induction lasted until HCR. Time to HCR was not specified for HR patients. For the whole intervention arm (n=62), median time to HCR was 32.5 days (14-54 days). For Kutny et al 2022, induction was from 28 days to a maximum of 70 days.

Glossary

Term	Definition
Adverse event	Any undesirable event experienced by a person while they are having a drug or any other treatment or intervention, regardless of whether or not the event is suspected to be related to or caused by the drug, treatment or intervention.
Bias	Systematic (as opposed to random) deviation of the results of a study from the 'true' results, which is caused by the way the study is designed or conducted.
Baseline	The set of measurements at the beginning of a study (after any initial 'run-in' period with no intervention), with which subsequent results are compared.
Case series	Reports of several patients with a given condition, usually covering the course of the condition and the response to treatment. There is no comparison (control) group of patients.
Clinical importance or significance	A benefit from treatment that relates to an important outcome such as length of life and is large enough to be important to patients and health professionals. As an example, it might include a general reduction in symptoms, less pain or improved breathing. Effects identified as statistically significant are not always clinically significant, because the effect is small or the outcome is not important. For example, if a treatment might lower blood pressure but there may be no evidence that this leads to an important clinical outcome, such as a lower risk of stroke or heart attack.
Comparator	The standard (for example, another intervention or usual care) against which an intervention is compared in a study. The comparator can be no intervention (for example, best supportive care).
Confidence interval	A way of expressing how certain we are about the findings from a study, using statistics. It gives a range of results that is likely to include the 'true' value for the population. A wide confidence interval (CI) indicates a lack of certainty about the true effect of the test or treatment - often because a small group of patients has been studied. A narrow CI indicates a more precise estimate (for example, if a large number of patients have been studied). The CI is usually stated as '95% CI', which means that the range of values has a 95 in a 100 chance of including the 'true' value. For example, a study may state that 'based on our sample findings, we are 95% certain that the 'true' population blood pressure is not higher than 150 and not lower than 110'. In such a case the 95% CI would be 110 to 150.
Control group	A group of people in a study who do not have the intervention or test being studied. Instead, they may have the standard intervention (sometimes called 'usual care') or a dummy intervention (placebo). The results for the control group are compared with those for a group having the intervention being tested. The aim is to check for any differences. Ideally, the people in the control group should be as similar as possible

to those in the intervention group, to make it as easy as possible to detect any effects due to the intervention.

Cost effectiveness study An analysis that assesses the cost of achieving a benefit by different means. The benefits are expressed in non-monetary terms related to health, such as life years gained (that is, the number of years by which life is extended as a result of the intervention). Options are often compared on the cost incurred to achieve 1 outcome (for example, cost per life year gained).

Term	Definition
Follow-up	Observation over a period of time of a person, group or defined population to observe changes in health status, or health- and social care-related variables.
GRADE (Grading of recommendations assessment, development and evaluation)	A systematic and explicit approach to grading the quality of evidence and the strength of recommendations developed by the GRADE working group.
Minimal clinically important difference	The smallest change in a treatment outcome that people with the condition would identify as important (either beneficial or harmful), and that would lead a person or their clinician to consider a change in treatment.
Outcomes	The impact that a test, treatment, policy, programme or other intervention has on a person, group or population. Depending on the intervention, outcomes could include changes in knowledge and behaviour related to health or in people's health and wellbeing, the number of patients who fully recover from an illness or the number of hospital admissions, and an improvement or deterioration in someone's health, symptoms or situation.
PICO (population, intervention, comparison and outcome) framework	A structured approach for developing review questions that divides each question into 4 components: the population (the population being studied); the interventions (what is being done); the comparators (other main treatment options); and the outcomes (measures of how effective the interventions have been).
P value	The p value is a statistical measure that indicates whether or not an effect is statistically significant. For example, if a study comparing two treatments found that one seems to be more effective than the other, the p value is the probability of obtaining these results by chance. By convention, if the p value is below 0.05 (that is, there is less than a 5% probability that the results occurred by chance), it is considered that there probably is a real difference between treatments. If the p value is 0.001 or less (less than a 0.1% probability that the results occurred by chance), the result is seen as highly significant. However, a statistically significant difference is not necessarily clinically significant. For example, drug A might relieve pain and stiffness statistically significantly more than drug B. But, if the difference in average time taken is only a few minutes, it may not be clinically significant. See Minimal clinically important difference.

	If the p value shows that there is likely to be a difference between treatments, the confidence interval describes how big the difference in effect might be.
Prospective study	A research study in which the health or other characteristic of patients is monitored (or 'followed up') for a period of time, with events recorded as they happen. This contrasts with retrospective studies.
Randomised controlled trial (RCT)	A study in which a number of similar people are randomly assigned to 2 (or more) groups to test a specific drug, treatment or other intervention. One group (the experimental group) has the intervention being tested, the other (the comparison or control group) has an alternative intervention, a dummy intervention (placebo) or no intervention at all. The groups are followed up to see how effective the experimental intervention was. Outcomes are measured at specific times and any

Term	**Definition**
	difference in response between the groups is assessed statistically. This method is also used to reduce bias.
Standard deviation	A measure of the spread, scatter or variability of a set of measurements. Usually used with the mean (average) to describe numerical data.
Statistical significance	A statistically significant result is one that is assessed as being due to a true effect rather than random chance. See P value.

References

Included studies

- Kutny MA, Alonzo TA, Abla O, Rajpurkar M, Gerbing RB, Wang YC, et al. Assessment of arsenic trioxide and all-trans retinoic acid for the treatment of pediatric acute promyelocytic leukemia: a report from the Children's Oncology Group AAML1331 trial. JAMA Oncol. 2022;8(1):79-87.
- Shah G, Mikhail FM, Bachiasvili K, Vachhani P, Erba HP, Papadantonakis N. Outcomes of high-risk acute promyelocytic leukemia patients treated with arsenic trioxide (ATO)/all trans retinoic acid (ATRA) based induction and consolidation without maintenance phase: a case series. Hematol Oncol Stem Cell Ther. 2020;13(3):143-6.
- Wang HY, Gong S, Li GH, Yao YZ, Zheng YS, Lu XH, et al. An effective and chemotherapy-free strategy of all-trans retinoic acid and arsenic trioxide for acute promyelocytic leukemia in all risk groups (APL15 trial). Blood Cancer J. 2022;12(11):158.

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