Reference no: 2320
Publication date: 27 February 2025

Clinical Commissioning Policy:

Arsenic trioxide in combination with all-trans retinoic acid for the treatment of high-risk acute promyelocytic leukaemia (age 12 months and over) [2320]

Summary

Arsenic trioxide in combination with all-trans retinoic acid (ATRA) is recommended to be available as a routine commissioning treatment option for high-risk acute promyelocytic leukaemia (APML) within the criteria set out in this document.

Arsenic trioxide in combination with ATRA is not licensed for use in high-risk APML. Therefore, Trust policy regarding the use of off-label medicines applies.

Committee discussion

Please see Clinical Panel reports for full details of Clinical Panel's discussion.

The Clinical Priorities Advisory Group committee papers can be accessed here: www.england.nhs.uk/publication/arsenic-trioxide-in-combination-with-all-trans-retinoic-acid-for-the-treatment-of-high-risk-acute-promyelocytic-leukaemia/

What we have decided

NHS England has carefully reviewed the evidence to treat high-risk APML with arsenic trioxide in combination with ATRA. We have concluded that there is enough evidence to make the treatment available at this time.

The evidence review which informs this commissioning position can be accessed here: www.england.nhs.uk/publication/arsenic-trioxide-in-combination-with-all-trans-retinoic-acid-for-the-treatment-of-high-risk-acute-promyelocytic-leukaemia/

Links and updates to other policies

This document updates:

- NHS England has published a not for routine commissioning position for arsenic trioxide in high-risk APML: Not routinely commissioned - Arsenic trioxide for high-risk APML.

Plain language summary

About acute promyelocytic leukaemia

Acute Promyelocytic Leukaemia (APML) is a form of white blood cell cancer (leukaemia) and is the most aggressive type of leukaemia with a severe bleeding tendency and potentially fatal course. APML is often associated with a severe disturbance in blood clotting which results in both bleeding and clot formation. Early mortality in APML due to bleeding complications is a substantial problem affecting up to 30% of patients. Therefore, identifying APML early can prevent some of these complications from developing.

APML is categorised into low, intermediate and high-risk sub-groups. This is based on both the presence of a defect (mutation) of the Pro-Myelocytic Leukaemia/Retinoic Acid Receptor-alpha (PML/RARα) gene or t[15;17] translocation, and the number of white blood cells and platelets found in the blood. Patients who present with a white blood cell count of <10,000/µl are categorised as low and intermediate risk; if the white blood cell count is ≥10,000/µl, patients are termed high-risk. These patients are at significantly higher risk of relapse compared to intermediate or standard risk patients. A greater proportion of children than adults have the high-risk form of the disease at diagnosis.

About current commissioned standard treatment

In 2018, NICE recommended the use of arsenic trioxide in combination with all-trans retinoic acid (ATRA) (a derivative of Vitamin A) in low- and intermediate-risk APML in adults in line with the licence for arsenic trioxide. This was then extended to children with low- and intermediate-risk APML via the Cancer Drug Fund (CDF). This has now become standard care in low and intermediate risk APML in both adults and children and has replaced chemotherapy. Low- and intermediate-risk APML are therefore out of scope of this policy.

The only commissioned treatment for high-risk APML is anthracycline chemotherapy in combination with ATRA. This involves a hospital stay of around five to six-weeks for each cycle (four cycles), the need for an indwelling central line inserted under general anaesthetic, and is associated with long term complications, in particular reduced fertility.

About arsenic trioxide

Arsenic trioxide is a chemotherapy drug that causes cell death (apoptosis) of leukemic cells and degradation of the PML/RAR alpha gene. It is licensed, in combination with ATRA, in adults for low- and intermediate-risk APML. Arsenic trioxide is given intravenously over a 40-week regimen.

In high-risk APML, arsenic trioxide, in combination with ATRA, is proposed to be given in place of anthracycline chemotherapy in combination with ATRA. Idarubicin (a type of anthracycline chemotherapy) may be given in combination with arsenic trioxide and ATRA, plus or minus steroids, during the induction phase only (induction phase lasts 60 days). Arsenic trioxide is given in combination with only ATRA during the consolidation and maintenance phase as an outpatient day case. Treatment with arsenic trioxide should be initiated as soon as possible after initial presentation to prevent major bleeding and associated complications.

The use of arsenic trioxide, in combination with ATRA, in both adults and children with high-risk APML is off-label.

Epidemiology and needs assessment

APML is a rare disease with fewer than 100 cases per year in the US and accounting for only 5-10% of paediatric acute myeloid leukaemia (AML) (Conneely et al, 2020) and 7-8% of adult AML cases (Cingam et al, 2023), with a peak in older adults.

The Children's Cancer and Leukaemia Group conducted an independent survey in 2022/23 of all children and teenage and young adults[1] (TYA) Principal Treatment Centres in the UK to determine the incidence of high-risk APML. It found that there were 52 cases of APML diagnosed in children up to their 18th birthday between the period 1st November 2013 to 31st October 2021. Of these, 23 cases were high-risk, equating to roughly 5 new cases in under 18s per year in England. The best population-based data to examine the change in incidence with age found that the incidence in those aged 18-39 was just less than twice that of those under 18 years at diagnosis (Burnett et al, 1999). Based on this information it is estimated by the policy working group that there would be a further 9 cases in the adult population leading to a total annual incidence of 14 patients.

Implementation

Inclusion criteria

All patients aged ≥12 months old[2] with newly diagnosed high-risk APML as confirmed by:

- a white cell count ≥10,000/µl (or 10 x 10^9/L)

  AND

- presence of the PML/RARα gene fusion by a fluorescence in situ hybridization (FISH) analysis or PCR

Exclusion criteria

Patients that meet **any** of the following criteria are excluded from treatment with arsenic trioxide:

- patient with isolated myeloid sarcoma (myeloblastoma, chloroma, including leukaemia cutis) but without evidence of APML by bone marrow or peripheral blood morphology
- patients with a pre-existing diagnosis of a prolonged QT syndrome (even if QTc is normal at the time of APML diagnosis), a history or presence of significant ventricular or atrial tachyarrhythmia, right bundle branch block plus left anterior hemiblock, bifascicular block
- patients on active dialysis for renal dysfunction
- female patients who are pregnant. Patients should not be pregnant or plan to become pregnant while on treatment[3]

[1] Cancer services in England are split into three commissioning groups: children (0-18 years old), teenage and young adults (TYA) (18-25 years old) and adults (>25 years). For the purposes of this policy, children refer to anyone under the age of 18 and adults refers to anyone over the age of 18.
[2] The age of this policy is restricted in line with the findings of the evidence review, as there is insufficient safety data for use of arsenic trioxide in children younger than 12 months old.
[3] There is an extremely high-risk of foetal malformation if pregnancy occurs while on ATRA in any amount, even for short periods.

- hypersensitivity to arsenic trioxide or ATRA

Starting criteria

Decision to initiate treatment in the acute setting must be agreed by a consultant haematologist who feels treatment with arsenic trioxide is the most appropriate treatment option for the patient. Treatment for children can only be started in a paediatric principal treatment centre. Treatment for teenagers and young adults (TYA) (<25 years old) should be overseen by a TYA principal treatment centre in accordance with the service specification for TYA cancer service specification (Children and TYA PTC Service Specification).

Patients should be discussed at an MDT prior to initiating treatment where time permits[4]. However, in urgent cases where this is not possible, patients should be subsequently discussed at a local multidisciplinary team (MDT) meeting. The meeting must involve at least two haematological consultants[5] who agree that continued treatment with arsenic trioxide is the most appropriate treatment plan.

Laboratory confirmation of white blood cell count **and** genetic confirmation of presence of PML/RARα gene fusion must have occurred prior to initiating treatment.

All patients must have a baseline ECG performed prior to starting treatment to rule out any cardiac abnormalities.

Women of childbearing potential must have a negative pregnancy test prior to starting treatment. Women of childbearing potential should be appropriately counselled regarding effective contraception for the duration of treatment.

Stopping criteria

A decision to stop treatment with arsenic trioxide should be made by the treating clinician if one of the following occur:

- a serious adverse event e.g., anaphylaxis or severe allergic reaction **OR**
- patient/family decides to stop treatment **OR**
- The MDT has not supported the decision to treat with arsenic trioxide

Patients should be assessed for evidence of treatment response by day 60 of treatment. If there is evidence of disease progression, treatment with arsenic trioxide should be stopped.

Patients should achieve complete molecular remission (CMR) after consolidation therapy. If CMR has not been achieved after completion of treatment, alternative treatment options should be sought.

Monitoring

A formal medical review to assess the response to treatment, and to determine whether the treatment should continue, should take place by day 60.

[4] Treatment with arsenic trioxide should be initiated as soon as possible after initial presentation to prevent major bleeding and associated complications. Continuation of treatment with arsenic trioxide should then be ratified at an MDT at the earliest opportunity.

[5] If arsenic trioxide is being used in a child then the MDT must include at least two paediatric haematology consultants and paediatric pharmacist

Patients should be reviewed regularly to assess ongoing tolerability of treatment with arsenic trioxide.

Electrolytes should be checked twice weekly, and an ECG performed weekly to monitor for any cardiac abnormalities developing in response to arsenic treatment.

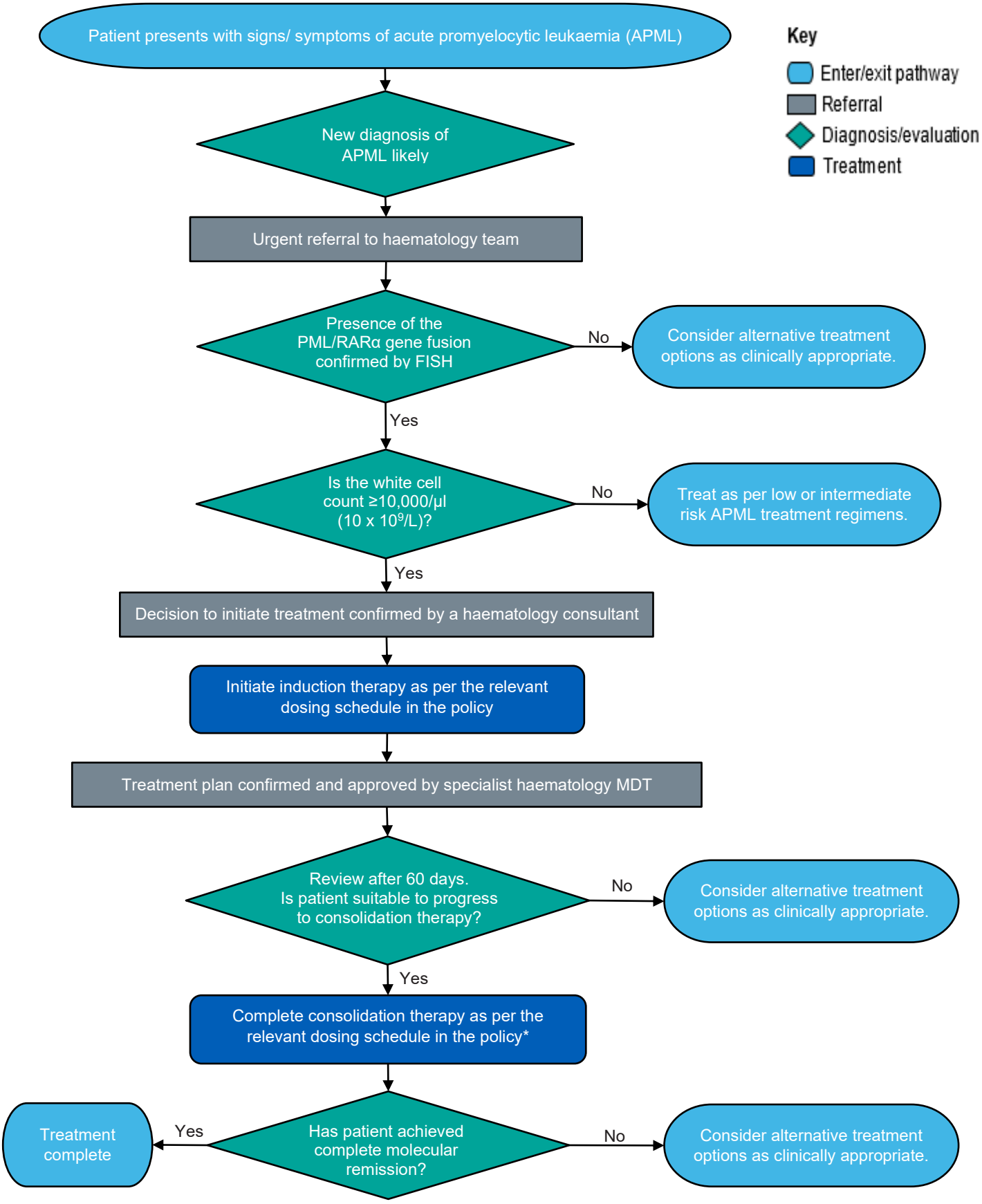
Dose

The use of arsenic trioxide, in combination with ATRA, for high-risk APML is off-label and Trust policy regarding off-label medicines should apply.

The treatment regimens have been agreed by the policy working group, based on the findings from the evidence review and the Guideline for the management of Acute Promyelocytic Leukaemia in Paediatric and TYA Treatment Centres, July 2022 and the AML17 phase 3 trial (Burnett et al, 2015, Russel et al, 2018).

The treatment regimens for arsenic trioxide, in combination with ATRA, for both paediatrics (12 months to <18 years) and adults (≥18 years) can be found below in Annex A.

Patient pathway



*For children this includes consolidation and maintenance therapy.
Please see Annex A for further details.

Governance arrangements

Provider organisations must register all patients using prior approval software and ensure monitoring arrangements are in place to demonstrate compliance against the criteria as outlined.

The use of arsenic trioxide is off-label; Trust policy regarding unlicensed medicines should apply.

Any provider organisation treating patients with this intervention will be required to assure itself that the internal governance arrangements have been completed before the medicine is prescribed. These arrangements may be through the Trust's Drugs and Therapeutics committee (or similar) and NHS England may ask for assurance of this process.

Mechanism for funding

Arsenic trioxide in combination with ATRA for high-risk APML will be commissioned and funded by NHS England under existing arrangements for the provision of Specialised Cancer Services.

Audit requirements

Data will be reviewed through use of prior approval forms and recorded via SACT database. The information is collected to inform future revisions of this policy.

Policy review date

This document will be reviewed when information is received which indicates that the policy requires revision. If a review is needed due to a new evidence base then a new Preliminary Policy Proposal needs to be submitted by contacting england.CET@nhs.net.

Our policies provide access on the basis that the prices of therapies will be at or below the prices and commercial terms submitted for consideration at the time evaluated. NHS England reserves the right to review policies where the supplier of an intervention is no longer willing to supply the treatment to the NHS at or below this price and to review policies where the supplier is unable or unwilling to match price reductions in alternative therapies.

Equality statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

- Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and
- Given regard to the need to reduce inequalities between patients in access to, and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities.

Definitions

Mutation	A change or alternation to genetic material. Mutations can result in altered function of the gene which can be harmful or beneficial. In cancer the mutations are usually harmful.
Translocation	A genetic problem in which material from a chromosome moves to another chromosome or is exchanged with material from it.
The National Institute for Health and Care Excellence (NICE)	NICE provides national guidance and advice to improve health and social care. NICE is an executive non-departmental public body, sponsored by the Department of Health and Social Care.

References

Burnett, A.K. et al. (2015) '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', The Lancet Oncology, 16(13), pp. 1295–1305. doi:10.1016/s1470-2045(15)00193-x.

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Cingam SR, Koshy NV. Acute Promyelocytic Leukemia. [Updated 2022 Jun 27]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK459352/

Conneely, S. and Stevens, A. (2020) 'Advances in pediatric acute promyelocytic leukemia', Children, 7(2), p. 11. doi:10.3390/children7020011.

James B, Kelly A, Ancliff P, McLelland V and Samrin-Balch L. (2022) *Guideline for the management of Acute Promyelocytic Leukaemia in Paediatric and TYA Treatment Centres*. Children's Cancer and Leukaemia Group

Russell, N. et al. (2018) 'Attenuated arsenic trioxide plus atra therapy for newly diagnosed and relapsed APL: Long-term follow-up of the aml17 trial', Blood, 132(13), pp. 1452–1454. doi:10.1182/blood-2018-05-851824

Annex A

Paediatrics (<18 years old)

1. Induction therapy

Induction lasts for 60 days (8.5 weeks). Arsenic trioxide and ATRA can be given with up to three doses of idarubicin[6] 12mg/m^2 on days 1, 3 and 5[7]. This should only be given during the induction phase.

Prednisolone/dexamethasone can be given as prophylaxis for differentiation as per local guidelines.

Induction therapy in children should only be carried out in a principal treatment centre[8].

Idarubicin and arsenic trioxide doses are not given together. Arsenic trioxide should only be started once the idarubicin has finished.

Week 1	ATRA 25mg/m^2/day orally in two equal divided doses daily Idarubicin 12mg/m^2 IV infusion over 1 hour given on days 1 and 3 and, if the WBC remains ≥ 10 x10^9/L a further dose of idarubicin 12mg/m^2 IV infusion over 1 hour is given on day 5 Arsenic trioxide 0.3mg/kg IV over 2 hours daily for days 1-5 (note the higher loading dose)
Week 2	ATRA 25mg/m^2/day orally in two equal divided doses daily Arsenic trioxide 0.25mg/kg IV over 2 hours twice a week, days 8 and 11 Prednisolone 0.5mg/kg/day oral in two divided doses daily to prevent differentiation syndrome to end day 14
Week 3-8	ATRA 25mg/m^2/day orally in two equal divided doses daily Arsenic trioxide 0.25mg/kg IV over 2 hours twice a week
Week 9	ATRA 25mg/m^2/day orally in two equal divided doses daily to end day 60

2. Consolidation therapy

Consolidation should commence 2 weeks after completion of the induction block and consists of cycles of ATRA and arsenic trioxide over 8 weeks.

Week 1	ATRA 25mg/m^2/day orally in two equal divided doses Arsenic trioxide 0.3mg/kg IV over 2 hours daily for 5 days (days 1-5) (note the higher loading dose)
Week 2	ATRA 25mg/m^2/day orally in two equal divided doses Arsenic trioxide 0.25mg/kg IV over 2 hours twice a week

[6] Hydroxy carbamide can be given to control the WBC count during the induction phase.
[7] If body surface area <0.6m^2 then the dose is 0.4mg/kg; this is not a dose reduction, this is the standard dose at this size.
[8] Supportive care can be given at a paediatric oncology shared care unit.

Week 3-4	Arsenic trioxide 0.25mg/kg IV over 2 hours twice a week No ATRA
Week 5-6	ATRA 25mg/m^2/day orally in two equal divided doses No arsenic trioxide
Week 7-8	No treatment; these are rest weeks

3. Maintenance therapy

Maintenance should continue on from completion of the consolidation block after the two rests weeks. It consists of 3 cycles of ATRA and arsenic trioxide over 20 weeks.

Cycle 1 (Weeks 1-8)

Week 1	ATRA 25mg/m^2/day orally in two equal divided doses Arsenic trioxide 0.3mg/kg IV over 2 hours daily for 5 days (note the higher loading dose)
Week 2	ATRA 25mg/m^2/day orally in two equal divided doses, daily Arsenic trioxide 0.25mg/kg IV over 2 hours twice a week
Week 3-4	Arsenic trioxide 0.25mg/kg IV over 2 hours twice a week No ATRA
Week 5-6	ATRA 25mg/m^2/day orally in two equal divided doses, daily No arsenic trioxide
Week 7-8	No treatment; these are rest weeks

Cycle 2 (Weeks 9-16)

Week 9	ATRA 25mg/m^2/day orally in two equal divided doses Arsenic trioxide 0.3mg/kg IV over 2 hours daily for 5 days (note the higher loading dose)
Week 10	ATRA 25mg/m^2/day orally in two equal divided doses, daily Arsenic trioxide 0.25mg/kg IV over 2 hours twice a week
Week 11-12	Arsenic trioxide 0.25mg/kg IV over 2 hours twice a week No ATRA
Week 13-14	ATRA 25mg/m^2/day orally in two equal divided doses, daily No arsenic trioxide
Week 15-16	No treatment; these are rest weeks

Cycle 3 (Weeks 17-20)

Week 17	ATRA 25mg/m^2/day orally in two equal divided doses Arsenic trioxide 0.3mg/kg IV over 2 hours daily for 5 days (note the higher loading dose)
Week 18	ATRA 25mg/m^2/day orally in two equal divided doses, daily Arsenic trioxide 0.25mg/kg IV over 2 hours twice a week
Week 19-20	Arsenic trioxide 0.25mg/kg IV over 2 hours twice a week No ATRA

Adults (≥18 years old)

1. Induction therapy

Induction lasts for 60 days (8.5 weeks). Arsenic trioxide and ATRA can be given with up to three doses of idarubicin[9] 12mg/m^2 on days 1, 3 and 5[10]. This should only be given during the induction phase.

Prednisolone/dexamethasone can be given as prophylaxis for differentiation as per local guidelines.

Week 1	ATRA 45mg/m^2/day orally in two equal divided doses[11], starting on day 1. ATRA treatment will be continued for a maximum of 60 days. Arsenic trioxide 0.30 mg/kg IV over 2 hours daily for 5 days (days 1-5) (note the higher loading dose)
Week 2-8	Arsenic trioxide 0.25mg/kg IV over 2 hours twice a week.

2. Consolidation therapy

ATRA: 45mg/m^2/day orally in two equal divided doses[11]. Treatment will be administered for 2 weeks on followed by 2 weeks off, for a total of 7 cycles (last cycle administered on weeks 25-26).

Course 1 (Week 1-8)

Course 1	
Week 1	Arsenic trioxide 0.30mg/kg IV over 2 hours daily for 5 days
Week 2-4	Arsenic trioxide will be given 2 days a week in a dose of 0.25mg/kg
Week 5-8	No arsenic trioxide

Course 2 (Week 9-13)

Week 9	Arsenic trioxide 0.30mg/kg IV over 2 hours daily for 5 days
Week 10-12	Arsenic trioxide will be given 2 days a week in a dose of 0.25mg/kg

[9] Hydroxy carbamide can be given to control the WBC count during the induction phase.
[10] If body surface area <0.6m^2 then the dose is 0.4mg/kg; this is not a dose reduction, this is the standard dose at this size.
[11] Rounded to the nearest 10mg increment.

Week 13-16	No arsenic trioxide

Course 3 (Week 17-24)

Week 17	Arsenic trioxide 0.30mg/kg IV over 2 hours daily for 5 days
Week 18-20	Arsenic trioxide will be given 2 days a week in a dose of 0.25mg/kg
Week 21-24	No arsenic trioxide

Course 4 (Week 25-32)

Week 25	Arsenic trioxide 0.30mg/kg IV over 2 hours daily for 5 days
Weeks 26-28	Arsenic trioxide will be given 2 days a week in a dose of 0.25mg/kg
Week 29-32	No arsenic trioxide