

**Clinical commissioning
policy statement:
Arsenic trioxide for the
treatment of high risk
acute promyelocytic
leukaemia (all ages)**

NHS England Reference: 170072P



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1 Plain language summary

Acute Promyelocytic Leukaemia (APML) is the most aggressive of all leukaemia related conditions. It is generally split into three groups – low, intermediate and high risk APML. A greater proportion of children have the high risk form of the disease.

The standard of care for patients with APML has until recently been all-trans retinoic acid (ATRA) (a derivative of Vitamin A) in combination with chemotherapy.

The National Institute of Health and Care Excellence (NICE) has recently considered the evidence for the use of a cancer medicine called arsenic trioxide (ATO) in combination with ATRA for low and intermediate risk APML in adult patients and considered the evidence sufficient to approve the combination for use in the NHS.

ATO is not licensed for use in high risk patients nor is it licensed for use in patients below the age of 18 years.

NHS England has considered the evidence for the combination of ATRA plus ATO in high risk AMPL and has concluded that there is insufficient evidence to support the commissioning of this treatment in this specific population at this time.

2 Background

APML is the most aggressive of all leukaemia related conditions. It is often associated with a severe disturbance in blood clotting which results in both bleeding and clot formation. Early mortality in APML due to haemorrhagic complications is a substantial problem affecting up to 30% of patients (Lehmann et al, 2011) and therefore identifying APML early can prevent some of these complications from developing.

APML is categorised, based on the number of white blood cells and platelets found in the blood, into three sub-groups: low, intermediate and high risk. Patients who present with a white blood cell out of $\leq 10,000/\mu\text{l}$ are categorised as low and intermediate risk; if the white blood cell count is greater than $10,000/\mu\text{l}$, patients are

termed high risk as they are at significantly higher risk of relapse compared to intermediate or standard risk patients.

The standard of care for all patients presenting with APML until recently has been all-trans retinoic acid (ATRA) in combination with chemotherapy, usually an anthracycline.

NICE have recently considered the evidence for the use of ATO in combination with ATRA in adult patients (Technology Appraisal TA526) and found sufficient evidence to approve the use of this treatment in the NHS, in line with its marketing authorisation, for:

- Untreated, low to intermediate risk APML in the first line setting; and
- Relapsed and refractory APML following first line treatment with chemotherapy and retinoid.

As ATO is not licensed for use in high risk patients nor is it licensed for use in patients below the age of 18 years, NICE did not consider its use in this population.

NHS England have reviewed the evidence for an ATO based regimen for high risk APML in all ages and have concluded that currently there is insufficient evidence to support the routine commissioning of ATO for the treatment of high risk APML (all ages).

3 Commissioning position

NHS England will not routinely commission all-trans retinoic acid in combination with ATO for the treatment of patients with high risk APML (all ages).

4 Effective from

17 August 2018

5 Evidence summary

The key evidence to support the proposal came from a National Cancer Research Institute (NCRI) sponsored trial – AML17 (Burnett et al) which published its findings in September 2015.

In the randomised controlled multicentre AML17 trial, eligible patients (aged ≥ 16 years) with APML, confirmed by the presence of the PML–RARA transcript and without significant cardiac or pulmonary comorbidities or active malignancy, and who were not pregnant or breastfeeding, were enrolled from 81 UK hospitals and randomised 1:1 to receive treatment with ATRA and arsenic trioxide or ATRA and idarubicin.

ATRA was given to participants in both groups in a daily divided oral dose of 45 mg/m² until remission, or until day 60, and then in a 2 weeks on–2 weeks off schedule. In the ATRA and idarubicin group, idarubicin was given intravenously at 12 mg/m² on days 2, 4, 6, and 8 of course 1, and then at 5 mg/m² on days 1–4 of course 2; mitoxantrone at 10 mg/m² on days 1–4 of course 3, and idarubicin at 12 mg/m² on day 1 of the final (fourth) course. In the ATRA and arsenic trioxide group, arsenic trioxide was given intravenously at 0.3 mg/kg on days 1–5 of each course, and at 0.25 mg/kg twice weekly in weeks 2–8 of course 1 and weeks 2–4 of courses 2–5. High-risk patients (those presenting with a white blood cell count $>10 \times 10^9$ cells per L) could receive an initial dose of the immune-conjugate gemtuzumab ozogamicin (6 mg/m² intravenously). Neither maintenance treatment nor central nervous system (CNS) prophylaxis was given to patients in either group. All patients were monitored by real-time quantitative polymerase chain reaction (PCR). Allocation was by central computer minimisation, stratified by age, performance status, and de-novo versus secondary disease.

The primary endpoint was quality of life on the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 global health status. All analyses are by intention to treat.

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235 patients were enrolled and randomly assigned to ATRA and idarubicin (n=119) or ATRA and arsenic trioxide (n=116). Participants had a median age of 47 years (range 16–77; IQR 33–58) and included 57 high-risk patients. Quality of life did not differ significantly between the treatment groups (EORTC QLQ-C30 global functioning effect size 2.17 [95% CI –2.79 to 7.12; p=0.39]).

Overall, 57 patients in the ATRA and idarubicin group and 40 patients in the ATRA and arsenic trioxide group reported grade 3 – 4 toxicities. After course 1 of treatment, grade 3 – 4 alopecia was reported in 23 (23%) of 98 patients in the ATRA and idarubicin group versus 5 (5%) of 95 in the ATRA and arsenic trioxide group, raised liver alanine transaminase in 11 (10%) of 108 versus 27 (25%) of 109, oral toxicity in 22 (19%) of 115 versus one (1%) of 109. After course 2 of treatment, grade 3 – 4 alopecia was reported in 25 (28%) of 89 patients in the ATRA and idarubicin group versus 2 (3%) of 77 in the ATRA and ATO group; no other toxicities reached the 10% level.

Patients in the ATRA and ATO group had significantly less requirement for most aspects of supportive care than did those in the ATRA and idarubicin group.

The authors concluded that ATRA and ATO is a feasible treatment in low-risk and high-risk patients with APML, with a high cure rate and less relapse than, and survival not different to, ATRA and idarubicin, with a low incidence of liver toxicity. However, they noted that there was no improvement in quality of life which was a key goal of the trial.

Whilst the evidence demonstrated a benefit on progression free survival there was no benefit on overall survival. In addition, there was no apparent increase in quality of life using the ATO-ATRA combination vs ATRA plus chemotherapy. Finally whilst children were included in the trial, the number who had high risk disease was not presented and the youngest child included in the study was 16.

6 Equality statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of this policy statement, 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.

7 Responsible CRG

Chemotherapy and Children and Young People's Cancer CRGs.

8 Date approved

8 August 2018

9 Policy review date

This document will be reviewed when information is received which indicates that the policy statement requires revision.

References

Burnett AK, Russeel NH, Hills, RK, Bowen D, Fell J, Knapper S, Morgan YG, Lok J, Grech A, Jones G, Khwaja A, Friis L, McMullin MF, Hunter A, Clark RE, Grimwade D; UK National Cancer Research Institute Acute Myeloid Leukaemia Working Group. *Lancet Oncol.* 2015 Oct; 16 (13): 1295-205.

Lehmann S, Ravn A, Carisson L, Antunovic P, Deneberg S, Möllgård L, Derolf AR, Stockelberg D, Tidfelt U, Wahlin A, Wennström L, Höglund M, Juliusson G. Continuing high early death rate in acute promyelocytic leukemia: a population-based report from the Swedish Adult Acute Leukemia Registry. *Leukemia* 2011; 25: 1128-1134.

National Institute for Health and Care Excellence (NICE). *Arsenic trioxide for treating acute promyelocytic leukaemia - Technology appraisal guidance (TA526)*. 2018. <https://www.nice.org.uk/guidance/ta526/resources/arsenic-trioxide-for-treating-acute-promyelocytic-leukaemia-pdf-82606843833541> [Accessed 5th July 2018]