AWTTC
All Wales Therapeutics & Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

Arsenic trioxide in combination with all-trans retinoic acid for the first-line treatment of high-risk acute promyelocytic leukaemia in adult patients unsuitable for anthracycline-based therapy

ONE WALES INTERIM COMMISSIONING DECISION

Arsenic trioxide in combination with all-trans retinoic acid for the first-line treatment of high-risk acute promyelocytic leukaemia in adult patients unsuitable for anthracycline-based therapy

Date of original advice: October 2016
Date of review: March 2019

The following Interim Pathways Commissioning Group (IPCG) recommendation has been endorsed by health board Chief Executives.

Arsenic trioxide in combination with all-trans retinoic acid can continue to be made available within NHS Wales for the first line treatment of high-risk acute promyelocytic leukaemia, characterised by the presence of the t(15;17) translocation and/or the presence of the Pro-Myelocytic Leukaemia/Retinoic-Acid-Receptor-alpha gene, in adult patients unsuitable for anthracycline-based therapy.

Arsenic trioxide is not licensed to treat this indication and is therefore off-label. Each provider organisation must ensure all internal governance arrangements are completed before this medicine is prescribed.

The risks and benefits of the off-label use of arsenic trioxide for this indication should be clearly stated and discussed with the patient to allow informed consent.

Providers should consult the General Medical Council Guidelines on prescribing unlicensed medicines before any off-label medicines are prescribed.

This advice will be reviewed after 12 months or earlier if new evidence becomes available.

Clinician responsibility
Clinicians will be obliged to collect and monitor patient outcomes. Evidence of clinical outcomes will be taken into consideration when reviewing the One Wales Interim Commissioning decision.

Health board responsibility
Health boards will take responsibility for implementing One Wales Interim Commissioning decisions and ensuring that a process is in place for monitoring clinical outcomes.

One Wales advice promotes consistency of access across NHS Wales.

This is a summary of new evidence available and patient outcome data collected, to inform the review.

Background
Acute promyelocytic leukaemia (APL) is a distinct subtype of acute myeloid leukaemia (AML) and presents clinically with coagulation disorders, which are associated with life-threatening haemorrhages. Arsenic trioxide was licensed in November 2016 for the induction of remission, and consolidation in adult patients with newly diagnosed low-to-intermediate risk APL (white blood cell count ≤ 10 x 10^3 per microlitre) in combination with all-trans retinoic acid (ATRA), characterised by the presence of the t(15;17) translocation and/or the presence of the Pro-Myelocytic Leukaemia/Retinoic-Acid-Receptor-alpha (PM-RARA) gene[1]. Arsenic trioxide is recommended for use in this indication by the National Institute for Health and Care Excellence (NICE)[2]. Treatment of high-risk APL remains off-label and is currently supported by One Wales Interim Commissioning advice[3].Clincians in Wales consider treatment to meet an unmet need and is a potentially curative option for a very small patient group.

Current One Wales Interim Commissioning Decision
Arsenic trioxide can be made available within NHS Wales to be used in combination with ATRA for the first-line treatment of APL, characterised by the presence of the t(15;17) translocation and/or the presence of the PM-RARA gene, in adult patients unsuitable for anthracycline-based therapy. February 2018[3]. This advice was partially superseded by NICE guidance in June 2018 (see Guidelines)[2].

Licence status
Arsenic trioxide in combination with ATRA for the first-line treatment of high-risk APL in adult patients remains off-label.

Guidelines
In June 2018, NICE recommended the use of arsenic trioxide in combination with ATRA for inducing remission and consolidation in acute promyelocytic leukaemia (characterised by the presence of the t[15;17] translocation or the PM/RARA gene) in adults with untreated, low-to-intermediate risk disease (defined as white blood cell count of ≤ 10 x 10^3 per microlitre)[2].

In August 2018, NHS England concluded not to routinely commission arsenic trioxide in combination with ATRA for the treatment of high-risk APL in patients of all ages, due to a lack of sufficient evidence[4]. The key evidence reviewed was from the AML17 study and is described in detail in the original One Wales evidence status report (August 2016)[5]. Whilst the evidence demonstrated a benefit on progression-free survival there was no benefit on overall survival[4]. Additionally, there was no apparent increase in quality of life using arsenic trioxide in combination with ATRA compared with ATRA plus chemotherapy. The AML17 study included patients aged 16 years and above, and did not report on the number of patients with high-risk disease[4].

Licensed alternative medicines
Anthracyclines may be used to treat high-risk APL. Where these are unsuitable, no new medicines have been made routinely available in NHS Wales for this indication since the original One Wales decision concerning arsenic trioxide.

Efficacy/Effectiveness
A repeat literature search found long-term follow-up results for one of the main multicentre clinical trials which included patients from Wales (AML17) and is described in the original evidence status report and previous review. Longer term results (median follow-up 67.4 months) from the AML17 trial, which randomised patients from all risk groups to receive either ATRA plus arsenic trioxide or ATRA plus idarubicin, are consistent with those previously reported[5,6]. Five-year survival was 92% in the ATRA plus arsenic trioxide group versus 86% in the ATRA plus idarubucin group (hazard ratio [HR] 0.71; 95% confidence interval [CI] 0.33 to 1.50; p = 0.4). A statistically significant reduction in frank relapse (1% versus 10% at 5 years; HR 0.18; 95% CI 0.05 to 0.6; p = 0.005) resulted in a statistically significantly higher relapse-free survival rate in patients with high-risk APL who received ATRA plus arsenic trioxide compared with those who received ATRA plus idarubicin (100% versus 83%; HR 0.12; 95% CI 0.02 to 0.84; p = 0.03)[6].

A retrospective, long-term follow-up (median 7.5 years) study investigating the efficacy of ATRA plus arsenic trioxide-based regimens compared with conventional ATRA plus chemotherapy regimen in newly diagnosed APL has been published[7]. The study was conducted in two hospitals in China and included patients aged 13 years and above. Patients (n = 690) were grouped according to their front-line regimens: ATRA plus arsenic trioxide with or without chemotherapy and ATRA with chemotherapy. Patients in the arsenic trioxide group showed superior 10-year estimated overall survival (93.9%; 95% CI 90.0 to 96.3; versus 89.1%; 95% CI 84.2 to 92.6; log rank P = 0.03) and 10-year estimated relapse-free survival (90.3%; 95% CI 86.6 to 93.0; versus 65.5%; 95% CI 58.9 to 71.3; log rank P < 0.0001) than patients in the ATRA plus chemotherapy group. Of the 690 patients, 141 had high-risk APL (120 patients in the arsenic trioxide group and 21 patients in the ATRA plus chemotherapy group). In subgroup analysis of patients with high-risk APL, the arsenic trioxide group had better 10-year estimated relapse-free survival (89.6%; 95% CI 81.0 to 94.4) compared with the ATRA plus chemotherapy group (74.7%; 95% CI 49.4 to 88.6; log rank P = 0.044). There was no statistically significant difference in overall survival between groups for the high-risk population. In the entire cohort, the incidence of secondary acute myeloid leukaemia/myelodysplastic syndrome was low and comparable between the arsenic trioxide and ATRA with chemotherapy groups[7].

Safety
No new significant safety issues were identified.

Cost effectiveness
A repeat literature search found no new cost-effectiveness evidence to that provided in the original evidence status report.

Budget impact
In Cardiff and Vale and Betsi Cadwaladr University Health Boards, no patients received arsenic trioxide for the treatment of high-risk APL in the last 12 months. Clinicians in Wales indicate that the number of cases is likely to be very small (1–2 per year) therefore it is possible that no patients may be treated in a specific year.

Impact on health and social care services
This remains minimal.

Patient outcome data
In Cardiff and Vale and Betsi Cadwaladr University Health Boards, no patients received arsenic trioxide for the treatment of high-risk APL in the last 12 months. Data from the remaining health boards have not been provided.

Next review date: February 2020

References

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