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

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

ONE WALES INTERIM COMMISSIONING DECISION PARTIALLY SUPERSEDED BY NICE GUIDANCE (TA526)
NICE GUIDANCE ISSUED MAY 2018

(Refer to NICE website for full details, including any specific restrictions on the use of the technology)

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Date of original advice: October 2016
Date of review: February 2018

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

Arsenic trioxide (TRISENOX®) in combination with all-trans retinoic acid can continue to be made available within NHS Wales for the first line treatment of 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 licensed for the treatment of low-to-intermediate risk acute promyelocytic leukaemia but is not licensed for high-risk acute promyelocytic leukaemia. As such, the latter indication is off label and remains outwith the NICE recommendation. 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. At the time of the One Wales Interim Commissioning decision arsenic trioxide (ATO) was licensed for the induction of remission and consolidation in adult patients with relapsed/refractory APL[1]. Use for the first-line treatment of this indication was off-label. A cohort of patients had been identified through data from individual patient funding request panels; based on unmet need within the service this medicine was considered to be suitable for assessment via the One Wales process.

Current One Wales Interim Commissioning Decision
Arsenic trioxide (TRISENOX®) can be made available within NHS Wales to be used in combination with all-trans retinoic acid (ATRA) for the first line treatment of APL, 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, in adult patients unsuitable for anthracycline-based therapy. October 2016.

Licence status
On 14 November 2016 a license extension was granted by the European Medicines Agency to include induction of remission, and consolidation in adult patients with newly diagnosed low-to-intermediate risk APL (white blood cell count [WBC] ≤ 10 x 10^9 per litre) in combination with ATRA, characterised by the presence of the t(15;17) translocation and/or the presence of the PM-RARA gene[2].

For high-risk APL (baseline WBC > 10 x 10^9 per litre), use of ATRA in combination with ATO remains off-label.

Guidelines
The National Institute for Health and Care Excellence (NICE) have proposed a single technology appraisal of ATO for the first line treatment of APL (ID446), a publication date is to be confirmed[3]. The All Wales Medicines Strategy Group (AWMSG) has received a submission from the marketing authorisation holder and is due to be appraised by AWMSG in May 2018[4].

Revised Canadian consensus guidelines for the treatment of older patients with AML recommend the use of ATRA with ATO for patients with low-intermediate risk APL[5]. High risk patients should also receive an anthracycline or, if not eligible, other cytoreductive therapy early during induction[5].

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.

Efficacy/Effectiveness
A repeat literature search found long term follow up results for the two main clinical trials (APL0406 and AML17) described in the original evidence status report[6,7]. Final results are published for the APL0406 clinical trial in patients with newly diagnosed APL of low-to-intermediate risk (WBC ≤ 10 x 10^9) randomly assigned to receive ATRA plus ATO or ATRA plus chemotherapy induction[8]. A total of 263 were evaluable for response to induction; 127 (100%) of 127 patients and 132 (97%) of 136 patients achieved complete remission in the ATRA plus ATO and ATRA plus chemotherapy groups respectively. Event-free survival (EFS) at 24 months was 98.3% (95% confidence intervals [CI] 95.9 to 100) and 86.8% (95% CI 81.1 to 92.8) in the ATRA plus ATO and ATRA plus chemotherapy groups respectively (p = <0.001). At 50 months EFS estimates were 97.3% (95% CI 94.3 to 100) and 80.0% (95% CI 72.9 to 88.0) respectively (p = <0.001)[8].

The primary outcome of non-inferiority of ATRA plus ATO over ATRA plus chemotherapy was confirmed[8]. The extended cohort of patients and prolonged follow up demonstrated significantly improved differences in all analysed outcomes: EFS, overall survival; disease-free survival; and cumulative incidence of relapse for ATRA plus ATO over ATRA plus chemotherapy. Health-related

quality of life outcomes confirmed those previously reported. Fatigue severity was significantly lower in the ATRA plus ATO arm compared to the ATRA plus chemotherapy arm after induction (p = 0.008), the only scale with a statistically significant overall difference between treatments[8].

Longer term results (median follow-up 53.4 months) from the AML17 trial which randomised patients from all risk groups to receive either ATRA plus ATO or ATRA plus idarubicin are consistent with those previously reported[9]. Five year survival was 93% and 87% in the ATRA plus ATO and ATRA plus idarubucin groups respectively. Relapse-free survival benefit was 96% versus 82% for treatment with ATRA plus ATO versus ATRA plus idarubicin respectively (hazard ratio [HR] 0.30 (0.13–0.67) p = 0.004). A non-statistically significant benefit of ATRA plus ATO over ATRA plus idarubicin was shown in low-risk disease (95% versus 86%, HR 0.45 (0.17–1.20) p= 0.11) and a statistically significant benefit in was seen in high-risk disease (100% versus 69%, HR 0.10 (0.02–0.46) p = 0.003)[9].

Safety
A summary of long-term post-marketing safety data has been published since the original evidence status report for ATO. A total of 2,197 adverse event reports were collated from marketing to July 2016, of these 1,735 reports were classified as serious and 462 as non-serious. The overall safety profile was consistent with known toxicities[10].

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

Budget impact
Extrapolation of data from Cardiff and Vale and Abertawe Bro Morgannwg University Health Boards indicate that the number of patients treated with first line ATO in the past 12 months is in line with the budget impact of 5 patients estimated in the original evidence status report.

Impact on health and social care services
This remains minimal.

Patient outcome data
[Confidential data removed.]

Refernces

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