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

Azacitidine for the treatment of progressive angioimmunoblastic T-cell lymphoma (OW16)

September 2023

ONE WALES INTERIM DECISION

Azacitidine for the treatment of progressive angioimmunoblastic T-cell lymphoma

Date of original advice: July 2020
Date of review: July 2023

The following One Wales Medicines Assessment Group (OWMAG) recommendation has been noted by the All Wales Medicines Strategy Group (AWMSG) and ratified by Welsh Government

Using the agreed starting and stopping criteria, azacitidine can be made available within NHS Wales for the treatment of progressive angioimmunoblastic T-cell lymphoma.

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

Providers should consult the relevant guidelines on prescribing unlicensed medicines before any off-label medicines are prescribed.

This advice will be reviewed after 2 years 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 Medicines Assessment Group decision.

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

One Wales advice promotes consistency of access across NHS Wales.

Starting and stopping criteria for azacitidine for the treatment of progressive angioimmunoblastic T-cell lymphoma

These criteria have been developed with support from Consultant Haematologists in Wales.

Starting criteria:
Second and subsequent line therapy of patients with relapsed/refractory angioimmunoblastic T-cell lymphoma (AITL) that are not fit or suitable for intensification of therapy with a BEAM (carmustine [BCNU], etoposide, cytosine arabinoside [Ara-C] and melphalan) conditioned autograft. Azacitidine should only be considered if the patient is ineligible to enrol in a clinical trial.

Patients who satisfy the eligibility criteria will be prescribed azacitidine following consultation with the patient and/or carer taking into account potential adverse effects, cautions and contraindications. This consultation should be recorded in the patient's notes.

Azacitidine is prescribed at a dose of 75 mg/m^2, injected subcutaneously, daily for 7 days followed by a 21 day rest period. It may be appropriate to administer this treatment as 5 days on, weekend off, 2 days on, to avoid higher administration costs over the weekend.

The Cheson criteria is used to classify AITL response to treatment, the treatment goal is remission[1]. In summary, a complete response (CR) is defined as the disappearance of all evidence of disease, a partial response (PR) is a regression of measurable disease and no new sites. Stable disease (SD) is a failure to attain CR/PR or progressive disease (PD). PD or relapsed disease is an increase by ≥ 50% of measurable signs of the disease from nadir. Overall response rate represents both CR and PR[1].

Prescribers will be expected to provide outcome data on all patients who receive azacitidine treatment under the One Wales Medicines process.

Stopping criteria:
Treatment should be reviewed after three cycles and azacitidine stopped if any of the following criteria are met:

- clinical evidence of disease progression/relapse in accordance with the Cheson response criteria[1].
- toxicity
- patient request

At 12 months treatment should be reviewed to consider whether there is continued clinical benefit for the patient and no evidence of disease progression.

Reference

1. Cheson B, Pfistner B, Juweid M et al. Revised response criteria for malignant lymphoma. *Journal of Clinical Oncology.* 2007;25(5):579-586.

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

Background: Angioimmunoblastic T-cell lymphoma (AITL) is a rare and often aggressive form of peripheral T-cell lymphoma. Signs and symptoms include generalised lymphadenopathy, skin rash, arthritis, polyclonal hypergammaglobulinemia and autoimmune conditions such immune thrombocytopenia. Typical frontline therapy is CHOP-like (cyclophosphamide, doxorubicin, vincristine, and prednisolone) chemotherapy, followed by BEAM (carmustine [BCNU], etoposide, cytosine arabinoside [Ara-C] and melphalan) conditioned autograft. AITL patients commonly relapse, and not all patients are eligible for BEAM conditioned autograft. Clinicians in Wales therefore considered there was an unmet need for the subset of relapsed or refractory patients not suitable or unfit for BEAM. This medicine was therefore considered suitable for assessment via the One Wales Medicines process.

Current One Wales decision: The subcutaneous formulation of azacitidine is supported for use for this indication.

Licence status: Azacitidine is not licensed to treat progressive (relapsed or refractory) AITL; its use in this indication is off-label. AWTTC is not aware of any plans to pursue marketing authorisation of azacitidine for this indication at this time.

Guidelines: There have been no new relevant guidelines or relevant updates to existing guidelines identified.

Licensed alternative medicines or Health Technology Assessment advice for alternative medicines: none. The NICE appraisal [ID3864] of oral azacitidine for treating relapsed or refractory angioimmunoblastic T-cell lymphoma was discontinued in December 2022 after the applicant company advised that marketing authorisation for this indication was no longer being pursued.

Effectiveness: A repeat literature search identified one retrospective study involving 15 relapsed/refractory AITL patients which assessed the efficacy of azacitidine (Yoon et al 2022). Among the 15 patients, 53.3% were younger than 60 years (n = 8). All patients had stage III/IV AITL and had received a median of three (range 1-8) previous lines of chemotherapy. Five of the patients received the prescribed dose of azacitidine, which was 75 mg/m^2 subcutaneously daily for seven consecutive days every four weeks until disease progression or medicine intolerance. Due to concerns over bone marrow function, the remaining 10 patients received a dose of < 175 mg/week.

The study calculated an overall response rate (ORR) using the sum of complete responses (CR) or partial responses (PR) seen in individuals. During the three-year study period, two CRs and four PRs were recorded (6/15, ORR 40%). Better responses were seen in patients who had received ≤ 2 prior chemotherapy lines (ORR 80% vs 20%), and the patients who received the prescribed 75 mg/m^2 also responded better than those who didn't (ORR 60% vs 40%). The median progression-free survival (PFS) was 1.6 months (95% CI 0.84-2.36) and the median overall survival (OS) was 10.5 months (95% CI 0.92-20.09). Patients who previously

had undergone ≤ 2 chemotherapy lines had better PFS compared with patients who previously received > 2 chemotherapy lines (P = 0.04). However, the OS was not significantly different between these two patient groups (P = 0.56).

The study concluded that azacitidine showed reasonable efficacy in the management of relapsed/refractory AITL. The clinical significance of this is uncertain due to the retrospective nature of the study, small sample sizes and the fact that the majority of patients did not receive azacitidine at the prescribed dose.

The final analysis of the ORACLE phase III study was published as a conference abstract in November 2022. Eighty-six patients with relapsed/refractory AITL or nodal follicular helper T-cell lymphoma were randomised between oral azacitidine (n = 42) and investigator's choice (gemcitabine [n = 24], bendamustine [n = 16] or romidepsin [n = 4]). Oral azacitidine was given at a dose of 300 mg/day (200 mg/day in Asian patients, based on previous phase I pharmacokinetics results) every day for 14 days out of 28 day-cycles, until disease progression or unacceptable toxicity. Patients had received a median of two (interquartile range 1-2) previous lines of treatment, 90.6% of them had stage III-IV disease. After 14.4 months follow up the primary endpoint of PFS was 5.6 months for oral azacitidine (95% CI, 2.66-8.11) vs 2.8 months (95% CI, 1.87- 4.83) in the standard arm (stratified log-rank test P = 0.0421), with a hazard ratio of 0.634 (95% CI, 0.38-1.07), which did not reach the required significance of P < 0.025. Median overall survival was 18.4 months (95%CI, 12.9-31.5) in the oral azacitdine arm vs 10.3 months (95% CI, 4.2-13.5) in the standard arm, with a hazard ratio of 0.557 (95% CI, 0.323-0.961).

Although oral azacitidine had a favourable safety profile compared to standard of care and was associated with prolonged overall survival, it did not meet the primary outcome of the study. This was attributed to an over-optimistic hypothesis of PFS improvement, resulting in a study which may have been underpowered to detect a clinically meaningful difference. The results have not been verified in a peer-reviewed publication.

Safety: The Yoon 2022 study analysed reasons for discontinuation of azacitidine treatment during the study period. Six patients discontinued treatment due to adverse effects; two with neutropenia, three with neutropenic fever (two also with sepsis) and one due to severe general weakness.

In the ORACLE study, the most frequent (> 40%) treatment emergent adverse events (TEAEs) for the oral azacitidine vs standard arm respectively were: blood and lymphatic system disorders (76.2% vs 93%) [neutropenia (42.9% vs 58.1%) and thrombocytopenia (23.8% vs 48.8%)], infections (35.7% vs 67.4%) and gastrointestinal disorders (71.4% vs 55.8%). At least one grade 3/4 TEAE occurred in 76.2% of patients in the oral azacitidine arm vs 97.7% in the standard arm, and at least one serious TEAE occurred in 26.2% of patients in the oral azacitidine arm vs 44.2% of patients in the standard arm.

These adverse reactions are included in the azacitidine SmPC. No new safety issues were identified.

Cost-effectiveness: No relevant cost-effectiveness analyses identified in the repeat literature search.

Budget impact: The estimated eligible population reported in the original evidence status report was five patients per year in Wales. Since the last review in July 2021, AWTTC is aware of [CONFIDENTIAL DATA REMOVED]

Impact on health and social care services: No new impact data have been provided, though we consider the impact of this medicine to be minimal.

Patient outcome data: [CONFIDENTIAL DATA REMOVED]. We welcome the data provided by clinicians.

Evaluation of evidence
We identified one retrospective review of 15 patients with AITL who were treated with off-label azacitidine and one phase III study comparing oral azacitidine with standard treatment based on investigator's choice. Overall there was some improvement on response rates and survival advantage with azacitidine but there are differences in the posology that mean comparison with previous studies is difficult. Outcome data show that the treatment has been of benefit to a small group of patients. The budget impact may be lower than originally estimated as fewer patients than predicted are receiving treatment. AWTTC recommends continuing to allow access in Wales to azacitidine as treatment for progressive angioimmunoblastic T-cell lymphoma.

Next review date: July 2025

References: a full reference list is available on request.

This document includes evidence published since the last review or full assessment of this medicine for the indication under consideration. It does not replace the original full evidence status report. Any previous reviews and the original full evidence status report are available on request by email to AWTTC@wales.nhs.uk.

Care has been taken to ensure the information is accurate and complete at the time of publication. However, the All Wales Therapeutics and Toxicology Centre (AWTTC) do not make any guarantees to that effect. The information in this document is subject to review and may be updated or withdrawn at any time. AWTTC accept no liability in association with the use of its content. An Equality and Health Impact Assessment (EHIA) has been completed in relation to the One Wales policy and this found there to be a positive impact. Key actions have been identified and these can be found in the One Wales Policy EHIA document.

Information presented in this document can be reproduced using the following citation: One Wales Interim Decision. Azacitidine for the treatment of progressive angioimmunoblastic T-cell lymphoma (OW16). 2023