AWTTC
All Wales Therapeutics & Toxicology Centre
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Evidence Status Report: azacitidine for progressive angioimmunoblastic T-cell lymphoma. (OW16)

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KEY FINDINGS

Report background

Angioimmunoblastic T-cell lymphoma (AITL) is a rare and often aggressive form of peripheral T-cell lymphoma (PTCL). Front line treatment is usually cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP)-like chemotherapy followed by BEAM (carmustine [BCNU], etoposide, cytosine arabinoside [Ara-C] and melphalan) conditioned autograft. AITL has very high relapse rates and there is no clear treatment pathway for relapsed/refractory AITL if the patient is not fit or suitable for BEAM conditioned autograft. There are no published guidelines for azacitidine's use as a treatment for AITL and its use for this indication is off-label. Clinicians in Wales consider there is an unmet need and have identified a cohort of patients who could benefit from this treatment. This medicine was therefore considered suitable for assessment via the One Wales process.

Efficacy/Effectiveness

The evidence of clinical effectiveness of azacitidine to treat AITL comes from individual case studies. Most of the case studies showed an improvement in complete and overall response rates as well as overall survival.

Safety

No new safety signals have been observed for azacitidine for the treatment of relapsed/refractory AITL in patients unsuitable for BEAM conditioned autograft.

Patient factors

Azacitidine is administered by subcutaneous injection, daily for 7 days every 28 days, by a healthcare professional.

Cost effectiveness

There are no studies on the cost effectiveness of azacitidine for relapsed/refractory AITL.

Budget impact

Specialist clinicians consulted by the All Wales Therapeutics and Toxicology Centre (AWTTC) estimate that there are currently five people with AITL in Wales. Assuming six cycles of treatment (the median number of cycles used in the individual case studies) this would be associated with a cost of £34,296 per patient, depending on treatment response rates. [Confidential information removed]. The budget impact is subject to significant uncertainty.

Impact on health and social care services

Minimal increased use of existing services.

Innovation and/or advantages

Azacitidine represents an option for people who have received front-line treatment for AITL and are unsuitable or not fit for a BEAM conditioned autograft.

BACKGROUND

Target group

The indication being considered is treatment of relapsed/refractory angioimmunoblastic T-cell lymphoma (AITL) for patients that are not fit or suitable for intensification of therapy with a BEAM (carmustine [BCNU], etoposide, cytosine arabinoside [Ara-C] and melphalan) conditioned autograft. There are no medicines currently licensed for the treatment of relapsed/refractory AITL.

Technology

The proposed mechanism of action of azacitidine is through hypomethylation of DNA and cytotoxicity on abnormal haematopoietic cells in the bone marrow[1].

Marketing authorisation date: Not applicable, off-label

Azacitidine is not licensed to treat relapsed/refractory AITL; its use in this indication is off-label. Azacitidine is licensed for treatment of patients who are not eligible for haematopoietic stem cell transplantation with: intermediate-2 and high-risk myelodysplastic syndromes; chronic myelomonocytic leukaemia (CMML) with 10—29% blasts without myeloproliferative disorder; acute myeloid leukaemia (AML) with 20—30% blasts and multi-lineage dysplasia; or AML with >30% blasts[1].

Dosing

There is no agreed dosing regimen for azacitidine to treat AITL. The recommended dose for myeloid disorder is 75 mg/m^2, injected subcutaneously, daily for 7 days followed by a 21 day rest period[1]. Although limited to individual case studies, the dosing regimens used in the literature for AITL align with that outlined in the Summary of Product Characteristics (SPC).

Clinical background

Angioimmunoblastic T-cell Lymphoma (AITL) is one of the nodal peripheral T-cell lymphomas (PTCLs). PTCLs are heterogeneous diseases resulting from the malignant transformation of mature T or natural killer cells[2]. The PTCLs represent 10-15% of all non-Hodgkin lymphomas[3] and AITL constitutes between 13% and 24% of PTCLs[4]. AITL is difficult to diagnose and treat because of the presence of both B- and T-cell clones. It has a variable clinical course with autoimmune features[4].

AITL typically presents with systemic illness, characterised by B symptoms (weight loss, night sweats and fever [68-85%]) and generalised lymphadenopathy (76-97%), often mimicking an infectious process[4]. The majority of patients have hepatosplenomegaly (52-78%) and pruritus is seen in a quarter of patients. Polyarthritis (18%) and ascites/effusions (23-37%) are also relatively frequent[4].

Laboratory investigations often show the presence of anaemia (40-57%), eosinophilia (39%), and occasionally pancytopenia[4]. A significant proportion of patients have circulating autoantibodies (66-77%). Bone marrow involvement is observed in 61%. A number of autoimmune phenomena have been reported in association with AITL[4].

AITL commonly presents in older patients (median age 59–64 years), with prevalence similar in both genders[4]. It is usually characterised by an aggressive course and a poor response

rate to conventional chemotherapy, with a 5-year overall survival rate reported to be 33%[5]. Following relapse median overall survival is reported to be about 6 months[6]. Patients often die from infectious complications which makes delivery of aggressive chemotherapy difficult. Combination chemotherapy may be warranted once a diagnosis is made. However, patients have frequent and early relapses or die due to infections[4].

Incidence/prevalence

The annual incidence of AITL in the UK is in the order of 1 per million [4]. This would equate to 3-4 patients in Wales. These numbers are in accordance with Individual Patient Funding Requests (IPFR) data.

A specialist clinician consulted by the All Wales Therapeutics and Toxicology Centre (AWTTC) estimates there are currently 5-6 patients with AITL in Wales who may be suitable for treatment with azacitidine.

Current treatment options

The Cheson criteria is used to classify AITL response to treatment, the treatment goal is remission[7]. 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[7].

It is common for AITL to come back after being in remission. There is no well-defined treatment pathway for AITL, beyond frontline cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP)-like chemotherapy, for patients that are not suitable for intensification of therapy with a BEAM conditioned autograft.

British Committee for Standards in Haematology (BCSH, 2013) guidelines for AITL recommend that patients requiring therapy should be entered into available clinical trials where possible[4]. Outside of this CHOP or fludarabine, and cyclophosphamide (FC) would be considered as standard therapies. Immunomodulatory therapies such as steroids, ciclosporin, thalidomide and lenalidomide have some evidence of efficacy in chemo-refractory cases. Consolidation with auto-HSCT should be considered for patients with chemosensitive disease in first remission or after relapse[4].

A specialist clinician consulted by AWTTC indicated that off-label use of bendamustine is one management option currently being utilised in Wales. However, their experience is that bendamustine is poorly tolerated compared to azacitidine, especially in older, frailer patients. In pooled results from an open label, Phase II trial and a retrospective multi-centre study of bendamustine for refractory/relapsed T-cell lymphoma, the ORR (overall response rate) was 45-69%, for the AITL subgroup (n = 103)[8,9], Median duration of response was 3.3-3.5 months for the full populations (n=198). The most frequent adverse events in all patients were haematological including Grade 3 to 4 neutropenia which varied in frequency between studies (56 and 16.7%) and thrombocytopenia (38 and 22.4%)[8,9]. In the phase II trial twenty-three patients (38%) required red blood cell transfusions and 16 (27%) required platelet transfusions[8].

Current NICE guidance (2016) for the management of PTCL is to consider CHOP as a first line treatment and to consider consolidation with autologous stem cell transplantation (auto-SCT) for people with chemosensitive peripheral T-cell lymphoma (at least a partial response to first-line chemotherapy) who are fit enough for transplantation[10].

ESMO guidelines for relapsed/refractory nodal PTCL (2015) encourages inclusion into clinical trials[3]. Outside of this the guidance for unfit patients is monotherapy with off-label use of gemcitabine or bendamustine which are generally well-tolerated, with an ORR of approximately 50% but modest durations of response[3].

Guidance and related advice

For the treatment of AITL:

- British Committee for Standards in Haematology. Guidelines for the Management of Mature T-cell and NK-cell Neoplasms (Excluding cutaneous T-cell Lymphoma) [4].

For the treatment of PTCL, the wider umbrella group that AITL falls under:

- NICE guideline NG52. Non-Hodgkin's lymphoma: diagnosis and management[10].
- European Society for Medical Oncology. Peripheral T-cell lymphomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up (2015)[3].

SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

A comprehensive literature search conducted by AWTTC, identified 14 case reports. These are briefly described below.

Efficacy

Evidence supporting the efficacy of azacitidine monotherapy in AITL is limited to case studies. Lemonnier et al (2018) report on 12 cases, including two which had been published previously[2,11,12]. In this study 12 patients with AITL (five with concomitant myeloid neoplasm, and one with myelodysplastic syndrome [MDS]) were retrospectively analysed. Patients received 75 mg/m^2 azacitidine subcutaneously, daily for 7 consecutive days, every 28 days, until progression or unacceptable toxicity. The median treatment duration was 5.5 cycles (interquartile range [IQR], 3.75-17). Six (50%) patients received rituximab in addition to azacitidine due to the presence of Epstein-Barr virus replication or B-blasts. The median age was 70.5 years (IQR, 67.5 to 73.5 years). All but one had relapsed/refractory disease, with a median of 2 lines of previous therapies (IQR, 1.75 to 3). Ten of the patients had received CHOP-like therapy and one had received mini-CHOP. One treatment-naive patient received azacitidine as first-line therapy. A third of patients (4/12) had a poor performance status (Eastern Cooperative Oncology Group (ECOG) > 2) at azacitidine initiation, seven patients had an ECOG of 2 or less[2].

Six patients (50%) showed a complete response and 3 patients (25%) showed a partial response, yielding an overall response rate of 75%. Of the 6 patients who achieved complete response, 3 patients had 5, 6, 7 cycles respectively and 3 had 20, 25, 61 cycles respectively.[2]. After a median follow up of 27 months the median progression-free survival was 15 months and median overall survival was 21 months. Five patients showed sustained response and complete remission more than 23 months after treatment was initiated. Three are still receiving treatment, whereas it was discontinued in the other two patients[2].

Gregory et al. (2019) reports a case of a 54-year old man with diagnosed AITL who had received 10 lines of failed therapies in which he had never achieved a complete remission[13]. He received 75 mg/m^2 azacitidine, subcutaneously, on days 1-7 of a 28-day cycle. The patient achieved a complete metabolic remission (CMR) after three cycles and at time of publication had ongoing CMR after 60 cycles of azacitidine[13].

Tobiasson et al, (2019) reports the case of an 86-year old woman with AITL and MDS who achieved complete remission following a total of six courses of CHOP[14]. The disease relapsed within 2 months and she was offered azacitidine 100 mg/m^2 on days 1-5 every 4th week. The patient started treatment in November 2017 and showed a complete response in January 2018. Azacitidine was continued until September 2018 when the patient was re-admitted due to a second AITL relapse. The patient died in November 2018[14].

Safety

The 12 patients described by Lemonnier et al. tolerated the treatment well[2]. Three out of 12 patients required transfusion, none developed febrile neutropenia. One patient experienced grade 2 neuropathy that was considered to be unrelated to treatment and another experienced unexpected digestive toxicity (grade 3 diarrhoea). There were no treatment related deaths or deaths due to myeloid neoplasm[2]. No safety data were reported in Gregory (2019)[13] and Tobiasson (2019)[14].

For patients with MDS, CMML and AML with 20-30% marrow blasts adverse serious drug reactions defined as very common and reported post marketing and during clinical trials included: febrile neutropenia (8.0%), thrombocytopenia (3.5%), pneumonia (2.5%) and anaemia (2.3%)[1]. The most commonly reported adverse reactions (≥ 30%) were: haematological reactions including thrombocytopenia; neutropenia and leucopenia (usually Grade 3-4); gastrointestinal events including nausea; vomiting (usually Grade 1-2) and injection site reactions (usually Grade 1-2). Rates of serious adverse events were higher for adult population aged 65 years or older with AML with > 30% marrow blasts with 25% reporting febrile neutropenia, 20.3% reporting pneumonia and 10.6% reporting pyrexia[1].

Clinical effectiveness issues

- There are no randomised control studies or systematic reviews investigating the use of azacitidine to treat relapsed/refractory AITL. The evidence is taken from individual case studies and anecdotal evidence from the submitting clinician.
- There are no published comparisons between azacitidine and bendamustine. From the limited data presented there appears to be similar response rates between treatments. Bendamustine may be associated with more haematological toxicities than azacitidine and clinical experts indicate that azacitidine is generally better tolerated than bendmustine.
- There is no published treatment protocol or recommended dose of azacitidine to treat relapsed/refractory AITL. The evidence from case studies indicates that the licensed dose for azacitidine for treating myeloid disorders, 75 mg/m^2 subcutaneously on days 1-7 every 28 days, is most widely used by clinicians. When reported, treatment duration varied widely in the studies, ranging from 2–61 cycles (at time of publication). It is difficult to get a consensus timeframe for treatment other than to continue azacitidine until progression or unacceptable toxicity.
- Patients with AITL presented in the case studies often had co-morbidities such as concomitant myeloid disorders and Epstein-Barr virus.
- Seven of the 12 patients reported in the Lemonnier paper received azacitidine as compassionate therapy for relapsed/refractory AITL in the absence of available therapy, or when such therapy was contraindicated, at the discretion of the physician, similar to the target group identified for this report.
- There is an on-going trial looking at oral azacitidine and relapsed/refractory AITL, results are expected to be available in 2022[15].

SUMMARY OF EVIDENCE ON COST-EFFECTIVENESS

There are currently no cost effectiveness data available.

BUDGET IMPACT

Clinical experts have indicated that the 75 mg/m^2 of azacitidine, injected subcutaneously, daily for days 1-7 in a 28 day cycle would be used in the treatment of progressive AITL. This guidance matches the SPC. Clinical experts confirm that in practice in Wales azacitidine is administered on consecutive weekdays only (5 days on, weekend off, 2 days on), thus avoiding the higher administration costs over weekends. In the absence of any consensus and guidelines, treatment was assumed to be 6 cycles based on the median number of cycles reported by Lemonnier. The list price of azacitidine (100 mg vial) is £321.00[16]. [Confidential information removed].

Clinical experts have suggested that the comparator, and therefore the displaced medicine, would be bendamustine 120 mg/m^2 by IV infusion on days 1 and 2 of a 28 day cycle. Treatment was assumed to be 6 cycles based on the method used in a study looking at bendamustine in relapsed/refractory T-cell lymphomas, which included 32 AITL patients[8].

It is assumed that all patients receive one set of six cycles and that all patients receive 100% of the dose. Vial wastage is assumed. No patients carry on treatment in to the following year.

Table 1 details the medicine and administration costs for azacitidine and bendamustine. This excludes VAT.

Table 1. Estimated annual acquisition costs in Wales (list price)

	Azacitidine*†§	Bendamustine*†¶
Net drug acquisition costs	£26,964	£7,453
Net drug administration costs	£7,332	£3,246
Overall net cost per patient	**£34,296**	**£10,699**

* This assumes a body surface area of 1.79 m^2.
† This assumes six cycles of treatment.
§ Assumes 'Deliver Simple Parenteral Chemotherapy at first attendance' followed by 6 consultant led clinical haematology outpatient appointments - National Schedule of Reference Costs (HRG code SB12Z)[17].
¶ Assumes 'Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance' followed by 'Deliver Subsequent Elements of a Chemotherapy Cycle' for the follow-up appointment - National Schedule of Reference Costs (HRG codes SB14Z and SB15Z)[17]

Table 2 shows the net budget impact assuming that all eligible patients receive azacitidine instead of the comparator, bendamustine (Scenario 1) or only half of the patients receive azacitidine and the remaining patients receive bendamustine (Scenario 2).

Table 2. Potential treatment scenarios (list price)

	Year 1	Year 2	Year 3
Number of people eligible for treatment	**6**	**6**	**6**
Total costs for azacitidine per year	£205,776	£205,776	£205,776
Total costs for bendamustine per year	£64,194	£64,194	£64,194
Scenario 1: Net cost assuming 100% displacement of comparator	£141,582	£141,582	£141,582
Scenario 2: Net cost assuming 50%* displacement of comparator	£70,791	£70,791	£70,791
*Assumes 3 patients treated in each arm			

Budget impact issues

- The budget impact is based on drug acquisition and administration costs. Any monitoring / additional palliation costs were considered to apply equally to new and displaced treatments.
- There is uncertainty as to the number of cycles that patients would receive. The budget impact is based on six cycles of azacitidine per patient. In case reports the number of cycles varied considerably, in the Lemonnier et al case series of 12 patients the number of cycles ranged from 3 up to 61[2].
- The analysis does not include costs of adverse events. Clinical experts report that bendamustine is poorly tolerated compared to azacitidine, especially in older, frailer patients which may incur additional resource costs not captured in the budget impact.

ADDITIONAL FACTORS

Prescribing unlicensed medicines

Azacitidine is not licensed to treat this indication and is therefore 'off label'. Providers should consult the General Medical Council Guidelines on prescribing unlicensed medicines before any off-label medicines are prescribed.

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