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Real-world data of azacitidine for relapsed/refractory nodal T-follicular helper cell lymphoma in 11 patients

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Relapsed or refractory (r/r) nodal T-follicular helper cell lymphoma of the angioimmunoblastic type is a rare disease with a dismal prognosis. This disease usually harbors mutations in epigenetic modifiers. A standard of treatment for an r/r disease is not known. Here, we report real-world data of 11 patients with a median age of 73 years, treated with azacitidine, a hypomethylating agent. Overall survival was 182 days. Five patients died from progressive disease; three were in complete remission after allogeneic stem cell transplantation; two were in complete remission, still receiving azacitidine; and one was under treatment for relapse. The treatment was well-tolerated despite the advanced age, and there was a high burden of comorbidities with a median hematopoietic cell transplantation-specific comorbidity index (HCT-CI) of 5, a score for identifying relevant comorbidities. However, a grade 3 or 4 hematological toxicity occurred in nine patients. Azacitidine may be a suitable treatment option for some patients with r/r nodal T-follicular helper cell lymphoma.

KEYWORDS

azacitidine, PTCL, orphan disease, nodal T-follicular helper cell lymphoma, angioimmunoblastic T-cell lymphoma, T-cell lymphoma

1 Introduction

Peripheral T-cell lymphomas (PTCLs) account for 5%–10% of all non-Hodgkin lymphomas (NHLs) (1, 2). Nodal T-follicular helper cell lymphoma (TFH lymphoma) is a rare subtype of PTCL, accounting for 18.5% of all PTCLs or approximately 2% of all lymphomas (2, 3). Subtypes are classified into angioimmunoblastic, follicular, and not

otherwise specified (NOS) (4, 5). The median age at diagnosis is 65 years, and 56% of patients are men (3). Approximately one-third of patients have bone marrow involvement.

Thus far, the outcome for this is poor. The 5-year overall survival (OS) for TFH lymphoma of the angioimmunoblastic type after anthracycline-based chemotherapy is approximately 32% (6). Nevertheless, anthracycline-based regimens like CHOP or CHOEP (cyclophosphamide, doxorubicin, vincristine, prednisone with or without etoposide) remain the standard of care in the first-line setting (7–9). The median OS of relapsed or refractory (r/r) disease is 7.7 months without stem cell transplantation (10). For relapsed or refractory disease, there is currently no established standard of care. One approach is conventional chemotherapy. Combination chemotherapy regimens like GDP (gemcitabine, cisplatin, dexamethasone), ICE (ifosfamide, carboplatin, etoposide), and DHAP (dexamethasone, high-dose cytarabine, cisplatin) or single-agent chemotherapy with gemcitabine or etoposide is commonly applied (10, 11). Another approach is the use of novel therapeutics like romidepsin, pralatrexate, and belinostat, which have demonstrated efficacy (12–15) but are not approved in many countries.

TFH lymphoma of the angioimmunoblastic type harbors mutations in the genes *DNMT3A*, *IDH2*, *RHOA*, and *TET2* in 26%–39%, 20%–45%, 53%–72%, and 33%–82% of cases, respectively (16–22). *DNMT3A*, *IDH2*, and *TET2* are involved in DNA and histone methylation, and recurrent mutations in these genes are key drivers of epigenetic deregulation in hematological malignancies.

Azacitidine (aza) acts as a hypomethylating agent and thus partially counteracts these epigenetic changes (23) and has been successfully applied to treat myeloid neoplasms (24, 25). Aza is available as an oral or subcutaneous formulation. The rationale behind this therapy is that hypermethylation silences tumor suppressors and aza reverses this effect. Furthermore, it was shown in a gene expression profile analysis that, especially in combination with romidepsin, aza changes the transcriptome, for example, through downregulation of metabolism or upregulation of genes involved in cell cycle arrest (26). Therefore, aza was tested for the treatment of r/r disease. Lemonnier et al. conducted a retrospective study demonstrating a median OS of 21 months in 12 patients receiving subcutaneous aza (27). Another retrospective analysis showed an OS of 10.5 months for 15 patients with r/r TFH lymphoma (28). Recently, Dupuis et al. reported a progression-free survival (PFS) of 5.6 months and a median OS of 18.4 months in a phase 3 study of oral aza in patients with r/r TFH lymphoma (29). In this prospective trial, grade 3 or 4 adverse events were seen in 76% of patients. The most common events were hematological side effects (anemia, thrombocytopenia, neutropenia). Others were infections, gastrointestinal disorders, and metabolism/nutrition disorders. Febrile neutropenia was only seen in one patient.

Furthermore, aza has been tested in combination with romidepsin, polychemotherapy (CHOP), or chidamide in combination or without gemcitabine/oxaliplatin with promising results (30–34).

Given the low incidence of TFH lymphoma, further real-world data on the safety and efficacy of aza are urgently needed. We address this need by reporting on 11 patients with TFH

lymphoma of the angioimmunoblastic type, treated with aza at our institution.

2 Materials and methods

All patients who were diagnosed with TFH lymphoma and were treated with aza between 2019 and April 2025 were included. The diagnosis was made using the immunohistochemistry panel staining CD3, CD4, CD8, PD-1, ICOS, CD10, BCL6, CXCL13, and EBV (for example, see the [Supplementary Data](#)). CD30 was stained in special situations. Confirmation of diagnosis was by reference pathology. Next-generation sequencing was performed for typical mutations, but clonal hematopoiesis was not tested in routine diagnostics. Aza was administered subcutaneously at a dose of 75 mg/m² for 7 days of each 28-day cycle in 10 patients, unless adverse events necessitated discontinuation. One patient received 300 mg of aza orally together with his DLBCL treatment.

Demographic and clinicopathologic variables were collected. These included age, sex, medical comorbidities, performance status, laboratory results, immunophenotype, cytogenetic and molecular genetic aberrations, organs involved, treatment line, treatment duration, post-remission, and relapse treatments. Outcome measures included best response as assessed by computed tomography (CT) or positron emission tomography (PET-CT), duration of response, OS as defined by time from start of treatment to death from any cause, PFS as defined by time from start of treatment to progression, recurrence, cause of death, and type and severity of adverse events according to the Common Terminology Criteria for Adverse Events (CTCAE v5.0). Data lock was on 16 May 2025. This analysis was reviewed and approved by our institutional ethics committee (#469/2024BO2).

For descriptive statistics, absolute frequencies and percentages were used for categorical variables, and the median, arithmetic mean, and range were used for continuous variables. The Kaplan–Meier estimator was used to analyze the probability of OS and PFS.

3 Results

3.1 Patient characteristics

Eleven patients have been treated with aza for r/r TFH lymphoma at our institution. Nine suffered from the angioimmunoblastic subtype, and two from the NOS subtype. The median age was 73 years. For detailed information about the patient characteristics, see [Table 1](#).

The median hematopoietic cell transplantation-specific comorbidity index (HCT-CI) was 5 (range 3–8). One patient suffered from two other lymphomas prior to the start of aza (PTCL, NOS, and EBV-positive atypical B-cell proliferation). Both cancers were in remission when aza was administered. Four patients suffered from EBV-positive diffuse large B-cell lymphoma (DLBCL) simultaneously with TFH lymphoma. In one of these patients, TFH lymphoma and DLBCL were treated simultaneously with aza and rituximab. In another patient, TFH lymphoma and DLBCL were

TABLE 1 Patient characteristics.

#	Sex	Age	Organs involved	Molecular alterations	HCT-CI	Line of therapy	Prior therapies	Stage
1	M	71	LN, tonsils, lung	TET2, RHOA	4	4	8x CHOP, VIP/HD-BEAM, DHAOx/HD-BEAM	IVA
2	F	74	LN, lung, bone	DNMT3A, TET2	8	3	7x BV, 7x Gem/Ox + 5x Gem mono	IVA
3	F	73	LN	RHOA, TET2	3	2	6x CHOP	IVA
4	M	82	LN, Waldeyer's tonsillar ring, lung, skin	ND	7	2	6x CHOEP	IVB
5	M	46	LN, skin, BM	RHOA, TET2	3	2	6x CHOEP	IVA
6	F	78	LN, spleen, BM	TET2, RHOA, IDH2, DNMT3A	6	2	2x miniCHOP + 4x CHOP	IIIB
7	F	83	LN	TET2	3	2	6x BV-CHP + radiatio	IA
8	F	61	LN, BM	TET2, IDH2, RHOA, DNMT3A	5	2	6x R-CHOP	IVB
9	F	61	LN, CNS	RHOA, TET2	3	3	5x R-CHOP, 3x MAT + 2x ICE	IVA
10	M	64	LN, spleen, liver, bone	None	7	2	4x CHOEP + 2x DHAP + HD-BEAM	IVA
11	M	79	LN	TET2, DNMT3A	6	1	–	IIIA

BM, bone marrow; BV, brentuximab vedotin; CHO(E)P, cyclophosphamide, doxorubicin, vincristine, (etoposide), prednisone; CNS, central nervous system; DHAOx, dexamethasone, cytarabine, oxaliplatin; F, female; Gem, gemcitabine; DHAP, dexamethasone, cytarabine, cisplatin, cytarabine; HCT-CI, hematopoietic cell transplantation-specific comorbidity index; HD-BEAM, high-dose chemotherapy carmustine, cytarabine, etoposide, melphalan; ICE, ifosfamide, carboplatin, etoposide; LN, lymph nodes; M, male; Ox, oxaliplatin; MAT, methotrexate, cytarabine, thiotepa; VIP, etoposide, cisplatin, ifosfamide.

treated simultaneously with pola-R-CHP (polatuzumab vedotin, rituximab, cyclophosphamide, doxorubicin, prednisolone) and oral aza. One patient with concomitantly diagnosed myelodysplastic syndrome (MDS) was treated with venetoclax in combination with aza.

3.2 Treatment

All patients received aza for relapsed or refractory disease off-label for this indication. The median number of treatment lines was 2 (range 2–4).

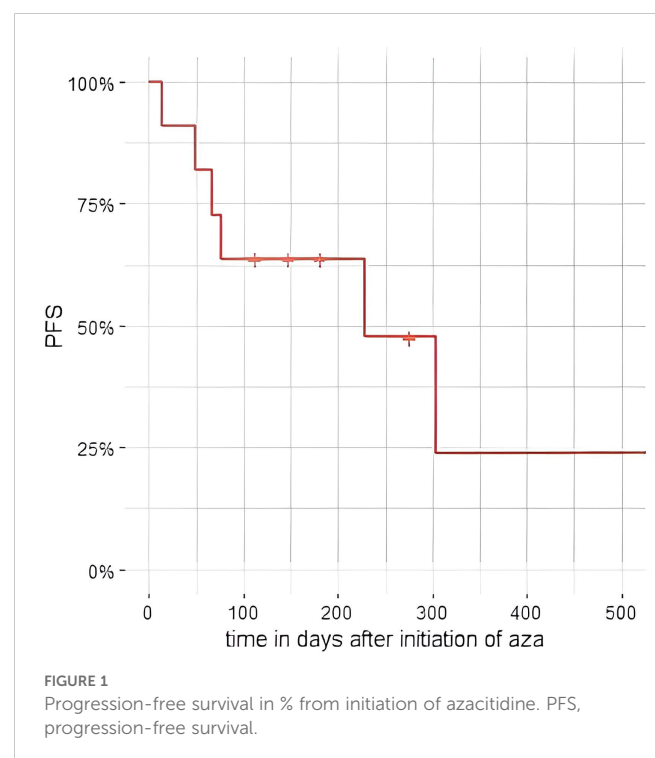
The median cycles of aza were 3 (range 1–10), and the median duration of aza treatment was 74 days (range 6–277 days). To date, two patients are still receiving aza. Three patients were treated with an allogeneic hematopoietic stem cell transplantation (alloHCT) for consolidation. Two were transplanted in partial remission (PR) and one in complete response (CR).

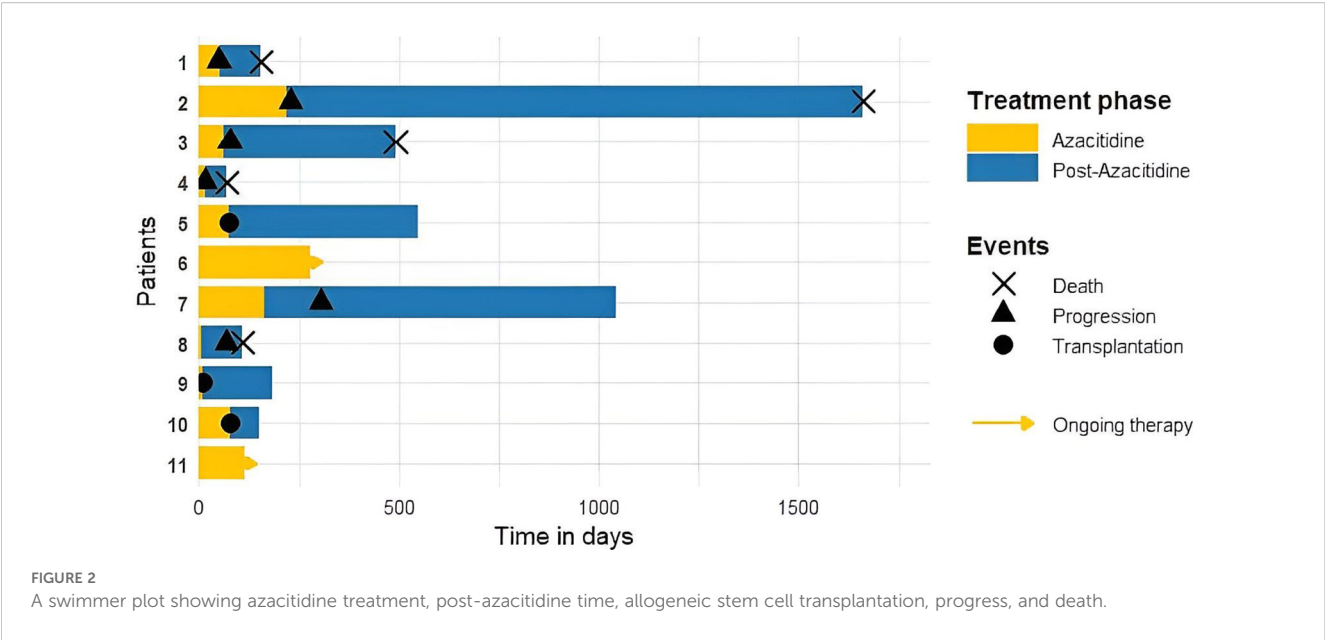
3.3 Safety and efficacy

In general, treatment with aza was well-tolerated. Eight patients developed neutropenia grade 3 or 4, four patients thrombocytopenia grade 3 or 4, and two patients anemia grade 3, respectively. Two patients suffered from a urinary tract infection. One patient had CMV reactivation and oral and esophageal candidiasis. The other patients did not develop major complications.

The complete response rate (CRR) was 36% and the overall response rate (ORR) was 64%. The median PFS was 149 days, and the median overall survival was 236 days (Figure 1). The patients

treated with an alloHCT are still alive without relapse. Two patients are still under treatment with aza and in CR after 5 and 10 cycles, respectively (Figure 2). These patients are 78 and 79 years old and have an HCT-CI of 6, which renders them ineligible for intensive chemotherapy or alloHCT. For progressive/relapsed disease under treatment with aza, the response to treatment was poor. All six





patients had progressive disease after further treatment. They received between one and four lines of therapy after aza (Table 2).

4 Discussion

In our cohort, we observed worse PFS and OS than in the phase 3 study of Dupuis et al. However, our cohort showed a more advanced age (73 vs. 69 years). Our patients also had significant comorbidities (median HCT-CI 5), and eight patients suffered from stage IV disease. Grade 3 or 4 hematologic events occurred in nine patients. However, only one patient suffered from serious infections (CMV reactivation and *Candida* infection). Interestingly, this

patient is still alive and in CR after alloHCT, underscoring the importance of alloHCT for consolidation.

The two patients who are still under treatment with aza without relapse were not eligible for intensive chemotherapy or alloHCT due to their age and comorbidities, underscoring the role of aza in this patient collective.

Retrospective and uncontrolled prospective studies show that despite the dismal prognosis of peripheral T-cell lymphoma, some patients achieve a long-term remission after alloHCT (35, 36). The only patients in our study being in CR after discontinued treatment received alloHCT, which is in line with our knowledge about the value of alloHCT.

The major limitation of our study is the small number of patients. Nevertheless, our study showed the clinical benefit of aza for patients

TABLE 2 Outcome and relapse therapy.

#	Cycles of aza	Best response	AlloHCT	PFS	OS	Relapse/refractory	Salvage therapy	Cause of death
1	2	PD	No	49	154	Yes	BV, Gem/Ox	PD
2	7	PR	No	228	1660	Yes	Cyclosporine A/prednisolone/IVIG, bendamustin, belinostat, dasatinib	PD
3	2	PD	No	76	491	Yes	BV/bendamustin, belinostat	PD
4	1	PD	No	14	69	Yes	Belinostat/valganciclovir	PD
5	3	PR	Yes	546	546	No	–	–
6	10	CR	No	277	277	No	–	–
7	6	CR	No	303	1041	Yes	Prednisolone	–
8	1	PD	No	67	108	Yes	Gem	PD
9	1	CR	Yes	182	182	No	–	–
10	4	PR	Yes	149	149	No	–	–
11	5	CR	No	113	113	No	–	–

AlloHCT, allogeneic hematopoietic stem cell transplantation; Aza, azacitidine; BV, brentuximab vedotin; Gem, gemcitabine; IVIG, intravenous immunoglobulin; OS, overall survival; Ox, oxaliplatin; PD, progressive disease; PFS, progression-free survival; PR, partial response.

with acceptable tolerability, and aza should be considered as an option for patients with r/r TFH lymphoma of the angioimmunoblastic type, especially if they are ineligible for intensive therapy.

Alternative therapies for patients who are ineligible for intensive chemotherapy and alloHCT are romidepsin, belinostat, and brentuximab vedotin. Romidepsin and belinostat are not approved in Europe for any indication, while brentuximab vedotin like aza is only approved for other indications. Therefore, in addition to the expected efficacy, availability must also be considered. While no head-to-head comparisons are available, the published retrospective series do not suggest a clearly superior choice among these agents. Belinostat showed an ORR of 25% with a median OS of 7.9 months in patients with a variety of PTCLs (12). In patients with THF lymphoma of the angioimmunoblastic type, the ORR was 54% and the PFS was 6.7 months for brentuximab vedotin (37). Romidepsin showed an ORR of 30% for this entity and a PFS of 4 months for all tested PTCLs (13). For aza, the results seem to be similar regarding PFS (5.6 months), but OS seems to be better (18.4 months) in a phase 3 trial (29). Nevertheless, our results did not prove these results. It should also be considered that comparisons between different studies can only be made with caution.

Because of the dismal prognosis of r/r TFH lymphoma of the angioimmunoblastic type and the lack of standard treatments, the approach of using the hypomethylating agent aza for a disease with mutations in epigenetic modifiers should be considered for combination therapy with other therapies to increase the survival of patients, either as a bridge to transplant for patients, who are eligible for alloHCT, or as palliative treatment for patients, who are ineligible for alloHCT.

Further research for the treatment of r/r TFH lymphoma is necessary. Aza offers a treatment approach, and some patients could benefit from aza or combinations of aza with other therapies.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Ethik-Kommission an der Medizinischen Fakultät der Eberhard-Karls-Universität und am Universitätsklinikum Tübingen. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

PF: Methodology, Formal analysis, Writing – original draft, Data curation, Investigation, Visualization, Writing – review & editing. JS: Methodology, Writing – review & editing, Validation.

AR: Writing – review & editing. CS: Writing – review & editing, Methodology. SK: Writing – review & editing. LP: Writing – review & editing. LM: Writing – review & editing. CL: Funding acquisition, Resources, Writing – review & editing. M-FH: Writing – review & editing, Supervision, Validation, Resources, Project administration, Conceptualization.

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Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/frhem.2025.1638236/full#supplementary-material>

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