

Evaluation and Management of Angioimmunoblastic T-cell Lymphoma: A Review of Current Approaches and Future Strategies

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Abstract: Angioimmunoblastic T-cell lymphoma (AITL) is a rare and complex lymphoproliferative disorder, clinically characterized by widespread lymphadenopathy, extranodal disease, immune-mediated hemolysis, and polyclonal hypergammaglobulinemia. Significant progress has been made in the understanding of AITL since its recognition as a clonal T-cell disorder with associated deregulation of B-cells and endothelial cells within a unique malignant microenvironment. However, as the responses to conventional chemotherapy have not been durable, prognosis with current treatment approaches has remained dismal. Here we review the clinical presentation, prognosis, and management of patients with AITL. We discuss recent developments in the understanding of the pathogenesis of AITL at a cellular and molecular level, including the implication of the follicular helper T-cell as the corresponding cell of origin, the roles of Epstein-Barr virus, B-cell deregulation, angiogenesis, and other signaling pathways in AITL, and the therapeutic implications of these findings. Finally, we discuss recent clinical trials and novel treatment approaches in the management of patients with AITL.

Introduction and Epidemiology

Originally described in 1974 as “immunoblastic lymphadenopathy” by Rappaport¹ and Lukes,² angioimmunoblastic T-cell lymphoma (AITL) is recognized in the current World Health Organization (WHO) classification as a peripheral T-cell lymphoma (PTCL) with distinct clinicopathologic features.^{3,4} Globally, AITL represents approximately 20% of all PTCLs,⁵ and accounts for roughly 2–5% of non-Hodgkin lymphomas (NHLs), with significant geographic variation in distribution and incidence.⁶ In a report by the International T-cell Lymphoma Study Group, AITL was found to be more prevalent in Europe, where it accounted for 28% of PTCL cases, compared to 15% in North America and 17% in Asia.⁷

Keywords

Angioimmunoblastic T-cell lymphoma, Epstein-Barr virus, targeted therapy

Characteristic	Frequency (% of patients)
Clinical Features	
Ann Arbor stage III or IV	81–97
B symptoms	64–85
ECOG performance status ≥ 2	46–72
Male gender	58–67
Bulky disease (≥ 10 cm)	26
Polyarthritis/arthralgias	12–18
Extranodal Presentations	
Splenic involvement/splenomegaly	55–73
Liver involvement/hepatomegaly	25–72
Bone marrow involvement	47–61
Skin involvement/rash	21–58
>1 extranodal site	46
Pleural Effusions/Ascites	26–42
Isolated extranodal site	1
Laboratory Features	
Hypergammaglobulinemia	50–83
Elevated serum LDH	66–76
Elevated beta-2 microglobulin	66
Anemia	40–65
Hypoalbuminemia	50
Hypogammaglobulinemia	50
Lymphopenia	42–49
Elevated ESR	45
Hyper eosinophilia	32–39
Positive Coombs test (with or without hemolysis)	9–33
Thrombocytopenia	20
Monoclonal gammopathy	8
Histopathologic/Molecular Features	
Presence of CXCL13 positive infiltrate	73–100
Presence of T-cell monoclonality	60–100
Presence of CD10 positive infiltrate	71–90
Presence of EBV positive B-cells	50–90
Presence of c-Maf positive infiltrate	60–75
Presence of B-cell monoclonality	0–80
Prominence of large cells (>10%)	26

Table 1. Frequency of Presenting Clinical Features in Patients with Angioimmunoblastic T-cell Lymphoma (AITL)

Data are summarized from presenting characteristics of over 800 patients with AITL as described in prior series assessing the prevalence of individual features.^{5,9,14,15,19,49,50,56,57,82,84,98-100}

The median age of patients within these studies ranged from 59 to 67 years. Not all features were annotated in all studies.

EBV=Epstein-Barr virus; ECOG=Eastern Cooperative Oncology Group; ESR=erythrocyte sedimentation rate; LDH=lactate dehydrogenase.

Clinical Features

Table 1 summarizes from several studies the frequency of presenting clinical findings in AITL patients. AITL typically affects older patients, with most patients diagnosed between the sixth and seventh decades of life, and most studies showing a slight male gender bias. The presenting features of AITL span a spectrum ranging from asymptomatic lymphadenopathy to a syndrome associated with severe systemic symptoms. Nonetheless, the constellation of symptoms at diagnosis often involves diverse constitutional indicators, including fevers, night sweats, arthralgias or arthritis, and weight loss.

More than 75% of AITL patients present with generalized lymphadenopathy.⁵ Extranodal involvement at diagnosis is common and typically manifests as hepato-splenomegaly, bone marrow involvement (in nearly half of patients), and pleural and pericardial effusions, though isolated extranodal involvement in the absence of nodal disease is exceedingly rare. A skin rash is frequently present, ranging from a maculopapular eruption to erythroderma to frank purpura, urticarial plaques, and papulovesicular lesions and nodules.⁸

Table 1 also summarizes laboratory abnormalities often found at presentation of patients with AITL. Notably, the presence of immunologic derangements is a hallmark, often presenting as polyclonal hypergammaglobulinemia, Coombs positive autoimmune hemolytic anemia (AIHA), cold agglutinins, cryoglobulins, as well as a number of other immunologic derangements including polyarthritis (both seronegative and seropositive) and thyroid disease.^{9,10} Despite the presence of this immune hyperactivity, AITL patients often exhibit immunodeficiency and a propensity for opportunistic infections prior to and during therapy.

Sites of both nodal and noncutaneous extranodal disease in AITL patients are reported as almost universally being hypermetabolic when assessed by (18)fluoro-2-deoxyglucose positron emission tomography (FDG-PET).^{11,12} However, the role of this imaging modality in this disease remains to be determined.

While roughly 10% of patients with AITL may experience an indolent clinical course and even spontaneous remissions,¹³ sustained remissions are rare and the majority of patients eventually succumb to their disease following a rapidly progressive course that is frequently fatal. In several series, the median survival of AITL patients has been estimated to be between 11 and 30 months, with only 30% of patients surviving more than 2 years.¹⁴⁻¹⁶

There are no independently validated prognostic models specifically stratifying risk for survival outcomes in AITL patients. Models such as the International Prognostic Index (IPI)¹⁷ and the Prognostic Index for T-cell Lymphomas (PIT)¹⁸ have been assessed in AITL, and in both of these schemes the majority of AITL patients present with high risk disease rendering these indices less useful than in the patient populations from which they were primarily derived (diffuse large B-cell lymphoma [DLBCL] and PTCL-*unspecified*, respectively). Notably, a recent study of 157 patients with AITL assessed both the IPI and the PIT and found neither able to reliably stratify risk in their population; multivariate analysis revealed male gender, anemia (hemoglobin less than 12 g/dL), and presence of mediastinal lymphadenopathy as independently predictive of overall survival in this cohort of AITL patients.¹⁹

Pathobiology

The characteristic histopathology of AITL spans a morphologic spectrum from atypical lymphoid proliferations to overtly malignant lymphomas with high-grade atypia. The involved lymph nodes demonstrate partial to complete effacement of the normal architecture with atretic or absent germinal centers and prominent neovascularization and polymorphous infiltration by plasma cells and immunoblasts.¹⁰ In this context, several distinct morphological patterns characterize AITL tumors,^{9,19} though a full discussion of the precise features of each subtype is beyond the scope of this review.

The lymph node architecture may reveal hyperplastic, depleted, or absent follicles. While peripheral sinuses are typically open and even dilated within involved nodes, the abnormal infiltrate often extends beyond the capsule into the perinodal fat. Early disease is often associated with intact and sometimes hyperplastic germinal centers with irregular borders, extrafollicular extension, and effacement of mantle zones paralleling disease progression.²⁰

Another prominent feature is extensive arborization of post capillary venules. These high endothelial venules (HEV)—many of which show thickened or hyalinized walls when highlighted by periodic acid-Schiff (PAS) staining—lie in an expanded meshwork of follicular dendritic cells (FDC) that extends outside follicles. These

expanded aggregates of FDCs, visible on immunostained sections, often have the appearance of “burned out” germinal centers. Large basophilic B immunoblasts and polyclonal plasma cells are observed in the parafollicular areas in 25–80% of patients, and these B-cells often harbor Epstein-Barr virus (EBV).^{20,21} Occasionally, Hodgkin-like proliferations are observed in AITL tumors, with binucleate or multinucleate cells reminiscent of Reed-Sternberg cells.¹¹ Despite the rare evolution of aggressive B-cell lymphomas in a subset of patients with AITL, neither an increase (>10%) in large atypical cells nor the presence of sheets of EBV-infected cells were found to affect survival of patients treated with chemotherapy.¹⁹

In its original description, AITL was known as immunoblastic lymphadenopathy and characterized by “a non-neoplastic hyperimmune proliferation of the B-cell system involving an exaggeration of lymphocyte transformation to immunoblasts and plasma cells.”^{22,23} However, a number of studies have since convincingly demonstrated the presence of a clonal proliferation of T-cells alongside the usually polyclonal or oligoclonal proliferation of B-cells (discussed below). Despite the strongly clonal pattern of T-cell receptor (TCR) rearrangements, neoplastic T cells are often rare and distributed in a reactive inflammatory background manifesting as a diffuse polymorphous paracortical infiltrate. Nonetheless, a distinct pattern of concurrent deregulation and proliferation of B-cells and endothelial cells characterizes the dynamic nodal and extranodal microenvironment and is a hallmark of AITL. As such, this unique pattern renders AITL *a forme fruste* of NHLs, with its diagnosis requiring methods that combine the morphologic, immunophenotypic, and molecular features of the tumor. Table 1 also summarizes the distribution of some of these histopathologic characteristics within tumors of AITL patients.

Immunophenotype

Despite the unique admixture of cell types within AITL, a coherent gene expression program typifies these tumors and allows their distinction from other PTCL tumors.^{24,25} Neoplastic cells within AITL frequently express a number of T-cell-associated antigens including CD3, and are usually positive for CD4 and for CD45RO, suggesting that memory helper T-cells are the originating cells.²⁶ Frequently surrounding the HEVs are expanded and extrafollicular clusters of FDCs that are highlighted by CD21 expression, where their presence is useful in distinguishing AITL from other T-cell lymphomas.²¹

The aberrant expression of CD10 by neoplastic T-cells is also frequently described in AITL, and is detectable both by flow cytometric and immunohistochemical methods.^{27,28} In one study where no CD10-positive cells

were observed in cases of PTCL-unspecified (PTCLu) or reactive lymphoid hyperplasia, CD10 positive T-cells were found in 27 of 30 AITL cases (90%) using immunohistochemical techniques.²⁷ Importantly, single-cell studies confirmed these CD10-positive cells as the neoplastic T-cells harboring the clonal TCR rearrangement.²⁷ Using flow cytometric methods, expression of CD10 on nodal T-cells has also been detected in nearly 60% of AITL cases.²⁹ These CD10 expressing T-cells are also frequently found within the peripheral blood, wherein on average 20% of circulating T-cells within most AITL patients have been observed to anomalously express CD10.³⁰

In addition to expressing CD10, the neoplastic T-cells also repeatedly express BCL6.^{28,31} BCL6 encodes a transcriptional repressor highly expressed in normal germinal center B-cells. This encoding is required for germinal center formation and is implicated in the pathogenesis of DLBCL, where it is frequently observed to be somatically mutated and/or involved within balanced translocations. Despite strong expression of BCL6 in AITL, such somatic mutations and balanced translocations of the BCL6 gene have never been described in AITL. Notably, BCL6 is also highly expressed in normal T-helper cells derived from germinal centers.³²

Reflecting the prominent endothelial cell contribution to AITL pathogenesis, high expression of vascular endothelial growth factor-A (VEGF-A) and its receptor vascular endothelial growth factor receptor 1 (VEGF-R1) has been observed both in tumor cells and associated endothelial cells in AITL.^{33,34} In this setting, high VEGF-A levels may be related to the burden of extranodal involvement and high levels of VEGF-A mRNA have been associated with adverse clinical outcome.^{33,34} Further, AITL T-cells also differ from normal T-cells in the expression of genes involved in matrix constitution, and adhesion.³⁵ For instance, the platelet derived growth factor receptor alpha chain (PDGFRA) is characteristically overexpressed in AITL, and may represent a therapeutic target.³⁵

More recently, T-cells were also found to express high levels of cytoplasmic CXCL13 with perinuclear enhancement in 90–100% of AITL cases, in comparison with 10–30% of PTCL cases.^{36,37} CXCL13 is a critical chemokine for B-cell entry to lymphoid follicles, allowing their arrest on HEVs. CXCL13 is also important in B-cell activation and in driving the proliferation of dendritic cells. Remarkably, CXCL13 is among the most highly and specifically expressed transcripts in normal T-helper cells derived from germinal centers.^{32,38} Additional markers of germinal center T-cells have also been observed to be expressed in AITL, including PD-1 and SAI.³⁹ This unique co-expression of markers typically characteristic of normal follicular T helper (T_{FH}) cells, has suggested derivation of AITL tumor cells from germinal center T-helper

cells.^{36,40} This hypothesis is also supported by the observation of broad similarities in genome-wide expression profiles comparing AITL tumor specimens with normal T_{FH} cells.^{25,35}

T- and B-cell Clonality Studies

Molecular studies of the TCR gamma chain and immunoglobulin heavy chain (IgH) within AITL have demonstrated that the vast majority (90%) have biased TCR rearrangements, with more than 75% of cases showing monoclonal pattern,^{21,41} and 14% an oligoclonal one.²¹ Of note, the detection of such clonal rearrangements of the TCR by polymerase chain reaction (PCR) can often be confounded by methods of tissue preservation, and retrospective studies of archival specimens preserved using formalin fixation and paraffin embedding methods have reported significantly lower estimates for the detection of clonality in these receptors.⁴¹

As a corollary to biased TCR rearrangements, studies of IgH also show the presence of biased IgH rearrangements in AITL, with 30–35% showing clonal patterns.⁴¹ These rearranged IgH loci frequently occur in EBV-infected B-cells that exhibit ongoing somatic hypermutation, suggesting a germinal center B-cell derivation.⁴² Furthermore, these unique B-cell clones not only survive, but they proliferate and expand alongside the clonal T-cell proliferation despite the frequent acquisition of crippling Ig mutations rendering them Ig-receptor deficient.⁴²

Though aggressive B-cell lymphomas such as DLBCL and Burkitt lymphoma can occasionally arise in patients with AITL, molecular evidence of clonal immunoglobulin rearrangement does not constitute sufficient proof of concomitant B-cell lymphoma or plasmacytoma, which typically manifest as sheets of monoclonal large B-cells in composite cases.¹¹

Karyotypic and Cytogenetic Features

Cytogenetic abnormalities have been described in almost 90% of patients with AITL,⁹ with roughly 60–70% of traditional metaphase karyotypes revealing clonal karyotypic anomalies.⁴³ Many tumors with such cytogenetic anomalies are described as harboring trisomy 3, trisomy 5, or both.^{43,44} Other described chromosomal abnormalities include a translocation between 7q35 and 14q11,⁴⁵ and trisomy X.⁴⁴ The prognostic significance of these cytogenetic aberrations was assessed in 50 AITL patients, where complex abnormalities and trisomy X were associated with adverse outcomes.¹³ Another study of 22 patients reported the most common abnormalities for AITL involving 5q (55%), 21 (41%) and 3q (36%) gains,

concurrent trisomies of 5 and 21 (41%), and loss of 6q (23%), with karyotypic complexity again predictive of worse overall survival.⁴⁶

More recently, sophisticated high resolution genotyping methods using microarrays have been applied to assess copy number alterations in AITL, including those associated with prognosis. One recent study showed copy number variation at 2q, 5p, 5q, and 17q to be statistically associated with the clinical outcome ($P < .01$).⁴⁷ Another study identified 6 genomic gains mapping at 5p15 and 22q11 as characteristic of AITL, and gain of 22q11 correlated with increased transcription of the LIF gene, previously characterized as part of the tumor cell signature in AITL.⁴⁸

Emerging Concepts in the Biology of AITL

Role of EBV

The vast majority (>90%) of AITL cases contain EBV-harboring cells, whether tested by immunohistochemical, in situ hybridization-based, or PCR-based assays.^{49,50} Despite some heterogeneity in the cellular pattern,⁴⁹ most of these EBV-harboring cells are B-cells⁵⁰ that express LMP-1 and EBNA2 antigens suggesting a type 2 or 3-like viral latency program.⁵¹ However, these B-cells differ from other EBV-immortalized B-cells in that they have the unusual capacity to survive and clonally expand despite their unusual immunoglobulin-receptor deficiency, normally a “forbidden” process.⁴²

Clearly, the emergence of such EBV-infected B-cell clones might be fostered by a paucity of surveillance mechanisms in the relatively immunodeficient state that typifies AITL. Accordingly, the emergence of such latently infected EBV-harboring B-cell clones may simply reflect a ‘bystander’ phenomenon. However, several lines of evidence support a possible pathogenic role for EBV within AITL: 1) EBV-harboring cells are detectable very early in the course of AITL⁵⁰; 2) transformed B-cells within AITL tumors have a unique immunoglobulin phenotype⁴²; 3) EBV is more frequently associated with clonal proliferations of B-cells in AITL⁴¹; 4) aggressive B-cell lymphomas harboring EBV arise in a subset of AITL patients^{20,51}; and 5) plasma EBV viral load correlates with histologic progression of AITL.⁵²

A Model for AITL Pathogenesis

These and other findings have led to speculative models of AITL pathogenesis, wherein EBV infection of B-cells plays a central, instead of a bystander, role. In one such model,⁵³ it is proposed that EBV-infected B-cells present EBV viral proteins (eg, EBNA-1) in the context of major histocompatibility complex (MHC) class II molecules. Simultaneously, through the EBV-induced expression of

CD28 ligand (B7),⁵⁴ these B-cells provide costimulatory signals for the activation of T_{FH} cells, and perhaps for their eventual antigen-driven transformation. TFH cells in turn express CXCR5 and CXCL13, with the latter chemokine promoting B-cell recruitment to the lymph node through adherence of B-cells to high endothelial venules (HEVs). This influx of B-cells leads to expansion and activation within the paracortex, where some B-cells become EBV transformed, and CD21-positive dendritic cells expand from the HEVs.

If EBV is indeed pathogenic in AITL, it may play this role in ‘hit-and-run’ fashion: After the evolution of a clonal proliferation of EBV-harboring B-cells, AITL tumor cells may continue to proliferate in cell-autonomous fashion independently of EBV. Nevertheless, given recent reports that plasma EBV viral load correlates with histologic progression of AITL,⁵² routine surveillance for the exacerbation of viremia seems prudent in potentially immunosuppressive regimens.

AITL Animal Models

Spontaneous AITL tumors arise in NZB/NZW F1 mice,⁵⁵ though the genetic basis of this phenotype remains unclear and it remains poorly characterized with little in the way of molecular, biochemical, or pharmacologic studies described thus far. Recently, another animal model of AITL was described, in which transgenic expression of c-Maf in the T-cell lineage of mice unexpectedly produced AITL tumors.⁵⁶ Strikingly, high expression of c-Maf has subsequently been observed in 60–75% of AITL cases.^{56,57} As a transcription factor and proto-oncogene, c-Maf is over-expressed in more than 50% of multiple myelomas and translocated in a subset of 5–10%.⁵⁸ In this context, c-Maf promotes proliferation and pathologic interactions of myeloma cells with bone marrow stroma through induction of VEGF.⁵⁸ In addition to promoting a hospitable niche through this angiogenic stimulation, c-Maf directly induces Cyclin D2 expression allowing bypass of the G1/S checkpoint and promotes plasma cell proliferation in multiple myeloma.⁵⁸ It is noteworthy that variable expression of a proliferation signature is also observed in PTCL tumors including AITL, wherein its expression has prognostic significance.⁵⁹

It is tempting to speculate on whether c-Maf overexpression in AITL T-cells modulates the proliferative index of tumors through modulation of Cyclin D and promotes a hospitable niche by induction of VEGF. Given the prognostic significance of angiogenesis and proliferation phenomena in AITL, c-Maf seems an attractive therapeutic target in AITL, as has been proposed in multiple myeloma.⁵⁸ Strikingly, a recent high-throughput screen for such c-Maf targeting compounds identified 24 corticosteroid derivatives among 2,400 off-patent drugs and

chemicals.⁶⁰ In this screen where glucocorticoids prevailed as c-Maf inhibitors through its proteasomal degradation, virtually no other class of compounds inhibiting c-Maf was identified.⁶⁰ Given the variable therapeutic efficacy of corticosteroids in AITL, identification of novel selective inhibitors of c-Maf likely requires broader chemical screens or structure-based drug design strategies. Conversely, differences of c-Maf expression levels in AITL tumors may underlie the variability of responses to corticosteroids that characterizes AITL patients.

The development of c-Maf–transgenic mice represents the only animal model of AITL thus far, and has important implications not only in elucidating the pathogenesis of AITL, but also an opportunity for the preclinical assessment of novel therapies for AITL.

Treatment

The lack of standard and effective treatments to date poses significant challenges for physicians treating patients with AITL. Given the rare nature of the disease, reports of treatment outcomes for AITL patients are rather limited in their number, design, and scope, where most approaches are extrapolated from the management of aggressive B-cell lymphomas. Significant responses have been described for single-agent therapy with corticosteroids,^{15,61,62} though typically productive for only short remissions. Anecdotal reports, small case series, and phase II studies have demonstrated short-term efficacy for a number of other agents both in untreated or relapsed patients with AITL. These include responses described for low-dose methotrexate (together with corticosteroids),^{63,64} fludarabine,^{65–69} cladribine,⁷⁰ interferon-alpha,^{71–75} thalidomide,^{76–78} lenalidomide (Revlimid, Celgene),⁷⁹ alemtuzumab (Campath, Bayer),⁸⁰ and denileukin diftitox (Ontak, Ligand Pharmaceuticals),⁸¹ among others. However, currently no consensus exists to determine if any of these agents improve outcomes more than conventional treatment. Accordingly, several of these agents are now the subjects of active investigation.

Within the limitations described above, we have attempted to summarize response and outcome data of a selected number of ‘AITL-focused’ studies, as well as broader ‘AITL-inclusive’ studies, which included at least 5 AITL patients. Responses of AITL patients to a variety of agents including cytotoxic drugs, combination chemotherapy regimens, immunomodulators, and monoclonal antibodies are represented in Table 2.

Chemotherapy

There is little consensus on the optimal chemotherapy regimen in either the frontline treatment of AITL patients or in the relapsed setting. Combination chemotherapy regimens have failed to significantly improve prognosis, with

multiple regimens having failed to increase the response and survival rate of patients with AITL to more than 30%. These regimens include vincristine, doxorubicin, and prednisolone (VAP);⁶¹ cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP)¹⁴ and CHOP-like regimens¹⁹; and cyclophosphamide, vincristine, prednisolone, bleomycin, doxorubicin, procarbazine, ifosfamide, methotrexate, and etoposide (COPBLAM/IMVP-16).¹⁵

Even though complete remission (CR) rates were higher in 39 patients receiving intense upfront combination chemotherapy (COPBLAM/IMVP-16, 64%) than in historical controls, the median survival observed for all patients was only 15 months, with 32–40% relapsing by 36 months.¹⁵ These results are similar to those of the CHOP-like regimen, with a CR rate of 60%, a relapse rate of 56% at a median follow-up of 46 months, and an overall 5-year survival of 36%.¹⁴

More recently, the Groupe d'Etude des Lymphomes de l'Adulte (GELA) reported their experience with 157 AITL patients, most of whom (n=147) were treated with CHOP-like regimens, with intensified courses in half of them.¹⁹ While nearly 30% of patients in this study were alive at 7 years after diagnosis, intensive therapies were not associated with improved survival.¹⁹

The data described above and summarized within Table 2 serve to illustrate several findings. While responses vary by agent, most described agents have significant success in achieving CR or partial remission (PR) in many AITL patients. Unfortunately, most of these responses are typically not sustained, and the majority of AITL patients relapse after a short remission. Accordingly, the median survival in most studies is shorter than 36 months, and generally less than 30–35% of AITL patients are alive at 5 years after the time of diagnosis, with most patients succumbing to infectious complications. Most of the patients with AITL described in large series have had treatment with anthracycline-based combination chemotherapy regimens. However, unlike DLBCL, there appears to be no significant difference in overall survival among AITL patients who did and did not receive an anthracycline.¹⁶

Targeted Therapies

As we discussed above, AITL tumors are characterized by derangements within an immunologic loop that involves a dynamic interplay between activated T-cells, B-cells, and endothelial cells, including overexpression of angiogenic factors such as VEGF. Many of the recent therapeutic strategies attempt to exploit immunomodulatory agents towards disrupting this loop. Such agents include cyclosporine, rituximab (Rituxan, Genentech/Biogen/Idex), and bevacizumab (Avastin, Genentech), among others, and the ongoing experience with their use in AITL is summarized in Table 2 and described below.

Table 2. Review of Selected Studies of Treatment Regimens for Patients with Angioimmunoblastic T-cell Lymphoma (AITL)

First author*	Regimen	Treatment Setting [†]	AITL/total (N)	ORR/CR [‡]	Median follow-up (months)	Outcome [‡]
Chemotherapy						
Siebert ¹⁵	COPBLAM/IMVP16	1st line	11/11	91/64	28	3 year OS, 28 %
Siebert ¹⁵	Prednisone +/- CT	1st & ≥2nd line	28/28	86/29	28	OS, 11 months
Pautier ¹⁴	CHOP-like	1st & 2nd line	33/33	NA/60	46	5 year OS, 36 %
Sallah ⁷⁰	Cladribine	≥2nd line	7/7	57/29	12	NA
Kadia ⁸²	CHOP-like	1st line	25/25	92/68	38	3 year OS, 57%
Arkenau ⁸³	GEM-P	≥2nd line	5/16	69/19	17	1 year OS, 68%
Park ⁸⁴	Anthracycline based	1st line	65/65	86/65	NA	5 year OS, 25%
Mourad ¹⁹	CHOP-like	1st line	147/147	NA/46	68	5 year OS, 33%
Targeted-therapy/Immunotherapy						
Pangalis ⁸⁵	Prednisone	1st & ≥2nd line	16/16	100/56	60	OS, 20 months
Siebert ⁷²	Interferon alpha	1st & ≥2nd line	12/12	67/33	NA	PFS, 3.5 months
Joly ⁸⁶	R-CHOP	1st line	9/9	89/NA	12	NA
Weidmann ⁸⁷	Alemtuzumab-FCD	1st & ≥2nd line	9/30	1st line: 63/58 ≥2nd line: 45/27	NA	NA
Advani ⁸⁸	Cyclosporine	≥2nd line	12/12	67/25	9	NA
d'Amore ⁸⁹	Zanolimumab	≥2nd line	9/21	33/11	NA	NA
Foss ⁸¹	Denileukin diftitox-CHOP	1st line	9/31	100/89	NA	PFS, 13 months
Reiman ⁷⁹	Lenalidomide	1st & ≥2nd line	4/10	50/NA	NA	NA

*Selected studies are chosen based on a primary focus of therapy for AITL and/or PTCL and inclusive of at least 5 patients with AITL.

[†]First line therapy is distinguished from therapies in the relapsed setting (2nd line and beyond).

[‡]Response assessments were not uniform across studies in terms of measurement modalities, timing, and durability. Outcomes for studies with median follow-up shorter than 1 year are considered immature and are reported as NA.

CHOP=cyclophosphamide, doxorubicin, vincristine, prednisone; COPBLAM/IMVP16=cyclophosphamide, vincristine, prednisolone, bleomycin, doxorubicin, procarbazine, ifosfamide, methotrexate, and etoposide; CR=complete response; CT=chemotherapy; FCD=fludarabine, cyclophosphamide, and doxorubicin; GEM-P=gemcitabine, cisplatin and methylprednisolone; NA=not reported/short follow-up duration; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; R-CHOP= rituximab + CHOP.

Cyclosporine Cyclosporine (CsA) is a potent immunomodulator that binds cyclophilin in T-cells and thus prevents the nuclear translocation of the nuclear factor of activated T-cells (NF-AT) and associated transcriptional response. As such, CsA potently inhibits T-cell activation and accordingly targets a central component of the

immune deregulation characteristic of AITL. We recently described our experience with the use of CsA in 12 patients with AITL and observed an overall response rate of 66% over a follow-up period of 2–120 months, with some responses being durable.⁸⁸ Based on the encouraging activity in our series and those described by others,

the efficacy and toxicity of CsA in refractory and relapsed AITL patients is being explored in an ongoing phase II clinical trial by the Eastern Cooperative Oncology Group (ECOG 2402). A potential concern of immunosuppressive therapy for AITL is exacerbation of EBV infection. If EBV is indeed centrally involved in the genesis and progression of AITL, one might envision that therapies such as cyclosporine that are primarily immunosuppressive could potentially exacerbate the natural history of the disease. Larger studies such as E2402 will potentially address this question.

Rituximab Based on the premise that B-cells may play a pathogenic role in AITL, Joly and colleagues recently described their experience with rituximab as an adjunct to CHOP (R-CHOP) in 9 elderly (age >60 years) patients with AITL.⁸⁶ Using R-CHOP given at standard doses, they noted CR in 8 of 9 patients, with 1 patient having progressive disease. At a median follow-up of 12 months, they reported 2 relapses at 13 and 14 months, with the 7 remaining patients in continued clinical remission. However, it is noteworthy that 5 of the 9 patients studied also harbored significant numbers of EBV-positive large B-cells and a serum M-protein, suggesting the presence of a B-cell clone that might be uniquely sensitive to rituximab. Their findings have been extended to an ongoing phase II study of the GELA group.⁸⁶

Bevacizumab Given the prominence of angiogenesis in AITL and the correspondingly high expression of VEGF-A and VEGF-R1 in these tumors, targeting this pathway has become an attractive concept, especially given the quantitative association of these markers with adverse outcomes in AITL patients. Case reports have suggested responses to bevacizumab,^{90,91} a monoclonal antibody targeting VEGF. The efficacy of combining bevacizumab with CHOP is being explored for upfront therapy in a phase II clinical trial (ECOG 2404).

Transplantation

The additive benefit of high-dose therapy with autologous hematopoietic stem cell transplantation (HDT-ASCT) as consolidative therapy in AITL patients is controversial. Inclusion criteria across studies have not been uniform and follow-up durations have been variable, making it difficult to extrapolate and compare observations across studies.

A retrospective study by Schetelig and associates in 29 AITL patients treated with HDT-ASCT reported 44% and 37% 5-year overall and progression free survival (PFS), respectively.⁹² Though the authors reported an increase in CR rate from 45% before HDT-ASCT to 76% after transplantation, these responses did not translate into durable remissions.

Rodriguez and coauthors⁹³ reported on 19 patients with AITL, most of whom received HDT-ASCT as front-line therapy. Of the 15 patients receiving HDT-ASCT in the front-line setting, 8 achieved CR, 2 achieved PR, and 5 had progressive disease prior to transplant. The authors reported an overall survival of 60% and PFS of 55% at 3 years; however, patients with refractory AITL prior to HDT-ASCT did not benefit from the procedure.

A more recent larger study by Kyriakou and colleagues⁹⁴ of the European Group for Bone and Marrow Transplantation (EBMT) described 146 patients with AITL who underwent HDT-ASCT in the relapsed setting or in second remission. At a median follow-up of 4 years, the authors reported an overall survival rate of 59% and a PFS rate of 42%. Remission status preceding HDT-ASCT was the most dominant predictor of outcome. PFS at 4 years for patients treated with HDT-ASCT in CR, as compared to those with chemosensitive or refractory disease, was 56% versus 30% or 23%, respectively.

All of these studies suggest that the benefit of HDT-ASCT is largely restricted to patients who are in remission at the time of transplantation or have chemosensitive disease. Nonetheless, the optimal timing of HDT-ASCT in AITL patients remains uncertain and prospective studies comparing transplantation in first CR versus delayed HDT-ASCT in patients with chemosensitive disease remain to be evaluated.

Allogeneic stem cell transplantation for patients with AITL has also been recently evaluated in a retrospective study of 11 patients, 9 of whom had received at least 1 or 2 prior regimens, and 8 of whom were in a CR prior to transplantation.⁹⁵ The authors reported a promising 5-year overall survival of 80% in this cohort of selected patients, which argues in favor of evidence for a graft-versus-lymphoma effect to this therapeutic strategy. Nonetheless, given the small number of patients in this study, conclusive interpretations as to the role of allogeneic HSCT in AITL are difficult to glean, with prospective trials designed to address this question still in need.

Conclusion

AITL is a distinct subtype of PTCL with unique clinical and pathobiologic features. A hallmark of the disease is the unique interaction between neoplastic and non-neoplastic cells and vasculature within the tumor microenvironment. Efforts to improve upon the standard therapy for AITL have arguably been hampered in part by gaps in our knowledge of AITL pathogenesis, with several central questions remaining to be addressed. These questions include a better understanding of the interactions among the unique mixture of cell types that comprise the microenvironment of AITL tumors, and the postulated cell of origin and its lymphoma-initiating properties.

Furthermore, a better understanding of the role of the EBV, angiogenesis, and bystander B-cells in the pathogenesis of this disease is likely central for the identification of key pathways and/or molecular targets that could be relevant for therapeutic intervention in AITL. Fortunately, emerging data in recent years now have started to address these questions, with important therapeutic implications, especially in guiding therapeutic strategies for immunomodulation and use of anti-angiogenic agents.

Based on the primary observations of the activity of several agents administered to AITL patients in small series, a number of therapeutic strategies are at the forefront of investigation within active clinical trials. These include strategies at targeting angiogenesis with agents such as bevacizumab, bolstered by the prognostic value of angiogenic factors in AITL, and emerging data regarding the activity of bevacizumab. Other strategies include immunomodulation with available agents such as cyclosporine and rituximab. Emerging preclinical data suggest other molecular targets and pathways for immunomodulatory therapy in AITL, such as c-Maf^{56,57} NF- κ B,⁹⁶ and Syk.⁹⁷

Further progress will require major collaborative effort to develop a rational therapeutic approach to AITL.

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