Angioimmunoblastic T-Cell Lymphoma Management

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Angioimmunoblastic T-cell lymphoma (AITL) is a frequent subtype of peripheral T-cell lymphoma (PTCL) that is clinically characterized by generalized lymphadenopathy, extranodal involvement, advanced stage at presentation, hypergammaglobulinemia, and significant immune dysregulation resulting in infections as the most common cause of death. Recent advances in pathobiology of AITL have improved our understanding of it as a clonal T-cell disorder and of its effect on B cells in the tumor microenvironment. Reponses to first-line therapies have largely been dismal. In this review, we discuss the clinical features, pathobiology, prognostic models, standard therapy, and newer therapeutic agents used and their implications for the future.
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Angioimmunoblastic T-cell lymphoma (AITL) is one of the most common forms of peripheral T-cell lymphomas (PTCLs) according to the World Health Organization classification of hematopoietic and lymphoid tissues and constitutes about one fifth of cases all over the world (Figure 1).[1,2] Geographically, it is more prevalent in Europe (29%) than North America (16%) or Asia (18%).[1,3] So far, no etiologic agents, risk factors, or racial predisposition have been identified.

AITL mostly affects the elderly population (median age, 59–65 years) with a slighter greater preponderance in males.[1,3] In most cases, AITL is manifested after exposure to medications (specially antibiotics), infection (viral/bacterial/fungal), or an allergic reaction suggesting abnormalities in immune regulation.[4] The most common presenting sign/symptom is generalized lymphadenopathy, which is often associated with B symptoms (fever, weight loss, night sweats).[5] This is followed by hepatosplenomegaly.[6] Bone marrow involvement (seen in up to 70% of patients) signifies a higher tumor burden and is often associated with a greater incidence of B symptoms, hepatosplenomegaly, and circulating tumor cells.[7] Up to 50% of patients present with a rash as some point during the course of disease.[6] Other dermatologic findings include nodular lesions, plaques, purpura, and urticarial lesions.[8] Less common signs and symptoms reported are arthralgias or arthritis, pleural effusion, ascites, pulmonary involvement, neurological involvement, and gastrointestinal involvement.[6,9] The majority of patients (90%) present with advanced disease (Ann Arbor stage 3–4).[10,11]

Common laboratory findings on presentation are hemolytic anemia (Coombs-positive), polyclonal hypergammaglobulinemia, and eosinophilia.[6,12] Other hematologic findings seen include thrombocytopenia, lymphopenia, elevated lactate dehydrogenase serum levels, elevated erythrocyte sedimentation rate, and an array of autoantibodies (rheumatoid factor, anti-nuclear antibody, anti-smooth muscle antibody).[6,12]

Histology of the involved lymph nodes is significant for partial to complete architectural effacement with near absence of germinal centers, prominent neovascularization, and small lymphocytes with cytological atypia clustered around high endothelial venules, in a background rich with plasma cells, histiocytes, epitheloid cells, eosinophils, immunoblasts, and follicular dendritic cells (FDCs).[13–16] The neoplastic $CD4^+$ T-cell clones are present in a minority of the lymph node infiltrate (5%–30%), and molecular analysis of these neoplastic cells suggests a T-helper cell (T_{FH}) phenotype expressing CD3, CD4, and CD10 molecules.[13] These malignant cells have striking predilection for cytoplasmic expression of the chemokine CXCL13, a marker specific for normal T_{FH} cells that is critical for recruitment of B cells and their activation in germinal centers.[17] While the specificity of CD10 positivity has been debated, CXCL13 is expressed in almost all AITL patients.[18–22] Other markers considered specific for T_{FH} cells are programmed death-1 (PD-1) receptor, inducible costimulator (ICOS), and BCL6 transcription factor.[23–27]

T-cell receptor gene rearrangements (TCRs) are present in about 80% of the $CD4^+$ clonal cells, and trisomy of chromosomes 3 and 5 is the most common cytogenetic abnormality observed in AITL.[16,28–31] Nearly all patients have Epstein-Barr virus (EBV)-infected B cells in the

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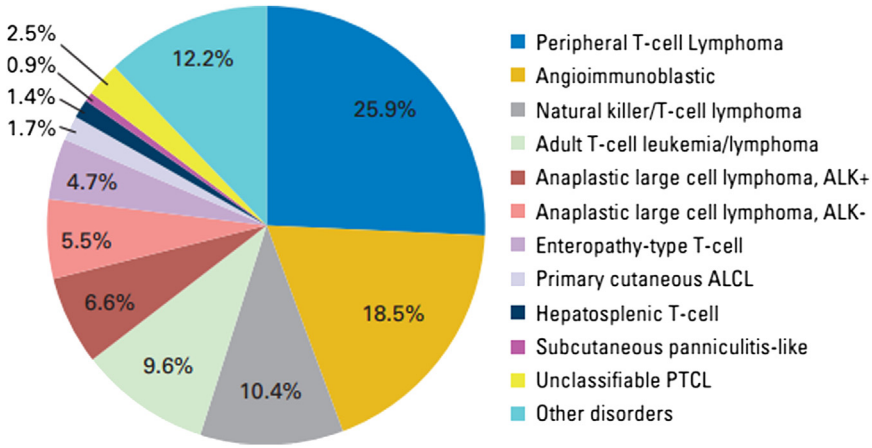

Figure 1. N=1,314 cases. ALCL, anaplastic large-cell lymphoma; PTCL, peripheral T-cell lymphoma; ALK, anaplastic lymphoma kinase. Data from Vose et al. J Clin Oncol. 2008;26: 4126-30; reprinted with permission.

lymph node, except for the neoplastic T cells.[32] It is possible that this viral infection or reactivation could be secondary to the underlying immune deregulation, or it could play a primary role in disease progression through paracrine mechanisms.[33] However, the presence of these EBV-positive cells has no influence on survival.[9] Gene expression signature of AITL is predominated by over-expression of B-cell– and FDC-related genes, chemokines, and their receptors, which provide a microcosm for the support of the T cell and contribute to angiogenesis and immunosuppression.[34] The gene signature contributed by the neoplastic T cells is very much similar to the ones expressed by T_{FH} cells, suggesting their role in some of the clinical features.[35,36] Gene expression profiling thus may help in diagnosis of cases that may have otherwise been classified as PTCL-not otherwise specified (NOS) by pathological findings alone.[34] Three different pathways that are significantly enriched on gene expression profiling that could be of potential therapeutic importance are the nuclear factor (NF)-κB pathway, the immunosuppressive pathway, and the interleukin (IL)-6 signaling pathway.[34]

The overall prognosis is poor and is associated with a median survival of less than 3 years, with long-term survival approaching 30% (Figure 2).[3,9] The International Prognostic Index (IPI) and the Prognostic Index for PTCL (PIT) have been of limited value in prognostication for AITL.[3,9] A simplified "prognosis in AITL" (PIAI) consisting of age >60 years, performance status >2, extranodal sites >1, presence of B symptoms, and platelets count $<150 \times 10^9$/L was able to differentiate a low-risk group associated with a 5-year overall survival (OS) rate of 44% and a high-risk group associated with a 5-year OS of 24%.[9,10]

THERAPEUTIC OPTIONS

A variety of regimens, whether as single agents or in combination, have been used for the treatment of AITL. While there are no best known options, anthracycline-based therapy is currently considered as the first line of treatment. AITL usually responds to this first-line therapy, but the effects are mostly short term and are associated with early relapse.[37] This knowledge is based on results of

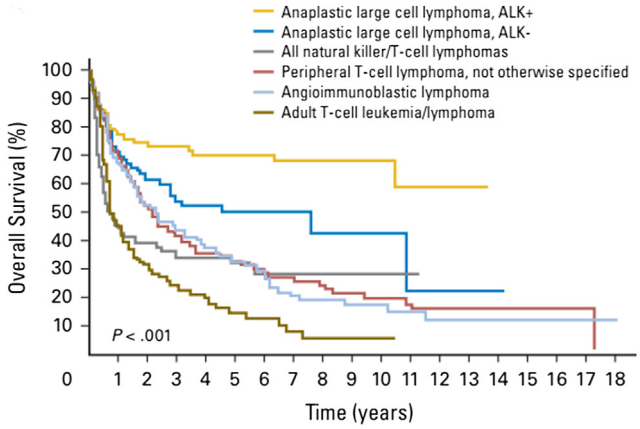

Figure 2. Overall survival in patients with common subtypes of peripheral T-cell lymphoma (PTCL). Data from Vose et al. J Clin Oncol. 2008;26:4126-30; reprinted with permission.

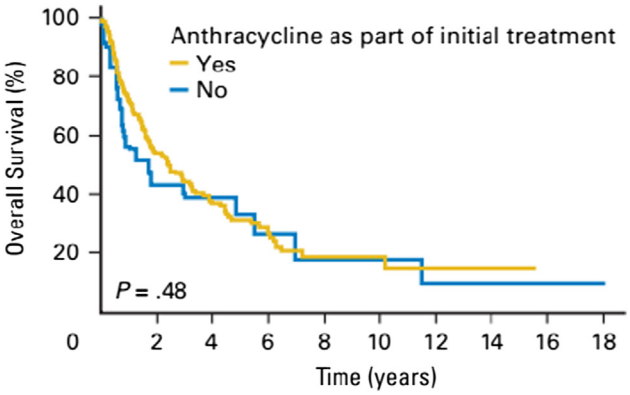

Figure 3. Overall survival in patients with angioimmunoblastic T-cell lymphoma (AITL) who were treated with or without anthracycline-based initial therapy. Data from Vose et al. J Clin Oncol. 2008;26:4126-30; reprinted with permission.

retrospective analysis of patients treated within the Groupe d'Etude des Lymphomes de l'Adulte (GELA) trials and findings from the T-Cell Lymphoma Project.[3,9] The 5-year OS for AITL patients treated with first-line therapy was 32%–33% (Figure 3).[3,9,10] There was no difference in OS when comparing different anthracycline-based regimens: ACVBP (dose-intense doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone), CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), or mBACOD (methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine, and dexamethasone).[3,9]

Cyclosporine is an immunomodulator that was tested in 12 AITL patients and found to disrupt the immune dysregulation.[38] With an overall response rate (ORR) of 75%, the results of this study formed the basis for a phase II trial of cyclosporine in recurrent or refractory AITL patients. However, the trial (NCT00070291) was stopped because of low accrual rates. Thalidomide is an immodulatory agent that acts on both B and T cells by inhibiting tumor necrosis factor (TNF), vascular endothelial growth factor (VEGF), IL-6, and NF-κB. It has been successful in maintaining clinical and radiologic remissions.[39] Based on these findings, a trial (NCT01553786) of CHOP in combination with lenalidomide has commenced in AITL patients.

Pralatrexate is an antifolate that is effectively internalized by tumor cells via reduced folate carrier, thereby depriving them of the natural folates necessary for synthesis of purines and pyrimidines. In a multicenter clinical trial of 111 patients with PTCL (13 with AITL) who had failed to respond to other chemotherapy regimens (70% were pretreated with CHOP), pralatrexate was administered with vitamin B_{12} every 8–10 weeks and folic acid daily.[40] The ORR was 29% in PTCL but only 8% (one partial response out of 13) in AITL patients.[40] Mucositis and thrombocytopenia were the most frequent side effects leading to withdrawal from treatment in 23% of patients.[40]

Romedepsin is a histone deacetylase inhibitor (HDACi) that induces acetylation of histones and nuclear transcription factors, resulting in growth arrest, cellular differentiation, and apoptosis. A multicenter phase II trial of romedepsin in relapsed or refractory PTCL showed an ORR of 38% with a median duration of about 9 months.[41] A response was observed in one of six (16%) patients with AITL.[41] Based on these findings, a phase III trial of romedepsin-CHOP has been initiated to test the long-term efficacy in PTCL patients (NCT01796002).

Belinostat is an HDACi tested in relapsed or refractory but HDACi-naïve PTCL patients. In this single-arm study, 122 patients underwent treatment with belinostat given as 3-week cycles until there was evidence of disease progression or unacceptable toxicity. Subgroup analysis of 22 confirmed AITL patients showed an ORR of 45%, progression-free survival of 6 months, and OS of 9 months. Three patients had dose reductions, two had adverse events resulting in discontinuation of therapy, and three patients discontinued therapy for unknown reasons. Considering the favorable safety profile of this drug, these results suggest the need for further evaluation of belinostat-based regimens.[42]

Rituximab is an anti-CD20 monoclonal antibody with activity against B cells. The numbers of B cells are significantly increased in the tumor microenvironment, which may sustain the presence of neoplastic T cells. In an effort to target the tumor microenvironment, a phase II clinical of 25 patients with AITL with good performance status (Eastern Cooperative Oncology Group [ECOG] ≤ 2) underwent treatment with rituximab in combination with CHOP.[43] The ORR was 80% (44% complete or unconfirmed complete response, 36% partial response) with a median response duration of about 2 years and a 2-year OS of 62%.[43] These results are promising, although a longer duration of follow-up is needed to determine the long-term clinical benefits of this combination.

Alemtuzumab (Campath-1H) is humanized immunoglobulin G1 antibody against CD52 antigen that is expressed on B and T cells irrespective of the malignant nature. Hypothetically, it seems a reasonable target against the tumor microenvironment of AITL patients. Although CD52 expression rates are less than 50% in PTCL, it provides a reasonable target for therapy.[44] In a phase II trial of alemtuzumab in combination with CHOP, 25 patients with newly diagnosed PTCL underwent treatment with this regimen. Of these patients, six (25%) had AITL and the ORR was 100% (6/6). The ORR in PTCL as a group was 75%, with a median duration of 11 months.[45] As expected, infectious complications were the most frequent nonhematologic toxicities observed (25%), albeit data on these are lacking for the AITL subtype. In another phase II study of 20 patients with newly diagnosed PTCL (three with AITL), Kim et al reported an ORR of 80% with a complete response rate of 65%.[46] Two of the three patients with AITL had complete responses and one had stable disease.[46] The estimated

OS at 1 year was 44%.[46] It was postulated that the OS was lower because of the high incidence of neutropenia (90%) and infection (cytomegalovirus reactivation) noted in this population despite adequate chemoprophylaxis, which led to earlier termination of the study after enrolling just 20 patients as compared to the original target of 43 patients.[46]

Bevacizumab is a monoclonal antibody targeting VEGF, which is highly expressed in AITL. While case reports have shown responses in this group of patients, the results of a trial (NCT00217425) comparing combination chemotherapy (bevacizumab-CHOP) are awaiting to be reported.[47,48]

Bortezomib is a proteasome inhibitor that acts by inhibiting the degradation of inhibitory kappa B (IκB) and the activation of nuclear factor-kappa B (NF-κB) and induces apoptosis in malignant T cells.[49] In a phase II trial evaluating the efficacy of bortezomib with CHOP in PTCL, complete responses were observed in 65% and the ORR was 76%.[50] Of the eight patients (17%) with AITL who underwent treatment with bortezomib and CHOP, five were alive without any evidence of disease. The 3-year OS for AITL patients was significantly better than that for the PTCL-NOS (non-specific) group. Neutropenia was the most common toxicity noted with this combination.[50] This combination was better with respect to the complete response rate and ORR when compared with another trial where bortezomib was combined with ACVBP (doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone) in untreated AITL and PTCL-NOS patients.[51]

Zanolimumab is a human monoclonal antibody directed against the CD4 antigen expressed in the malignant cells of AITL patients that kills them by T-cell receptor (TCR) inhibition and antibody-dependent cellular cytotoxicity.[52] A phase II trial treated 21 patients with refractory or relapsed PTCL (nine with AITL) with zanolimumab.[53] The ORR was 24% independent of histological subtype.[53] Of the nine AITL patients, two had a partial response and one had an unconfirmed partial response.[53] All three AITL patients who responded were females and had received 9–12 infusions of zanolimumab.[53] Despite the depletion of CD4 cells, infections were noted in three of 21 patients.[53]

Denileukin diftitox (DD) is a recombinant cytotoxic protein in which the IL-2 ligand is genetically fused to the diphtheria toxin. The IL-2 component binds to the IL-2 receptor (IL-2R)–expressing cells, thereby allowing the entry of the diphtheria toxin into the cells and inhibiting protein synthesis, eventually leading to apoptosis.[54] In a phase II trial of 27 patients with relapsed or refractory PTCL (three with AITL), the ORR was 48%.[55] Two of the three AITL patients achieved a partial response. Hypoalbuminemia, elevation of transaminases, peripheral edema, and skin reaction were the most common side effects noted. In another phase II trial by Foss et al evaluating the safety and efficacy of the combination of DD with CHOP in newly diagnosed PTCL patients, the ORR was 65% with a median duration of 30 months.[56] The median OS was not reported, and fatigue and nausea were the most common treatment-related adverse effects.

Salvage therapy has been tried with autologous stem cell transplant. High-dose chemotherapy (HDT) followed by autologous stem cell transplantation (ASCT) is associated with an improvement in response rate (76%) and a 5-year OS of 44% in PTCL.[57,58] When HDT/ASCT is given upfront in AITL, there is a higher complete response rate (56% at 4 years), but it is associated with a higher relapse rate (50% at 2 years).[57–59] However, the complete

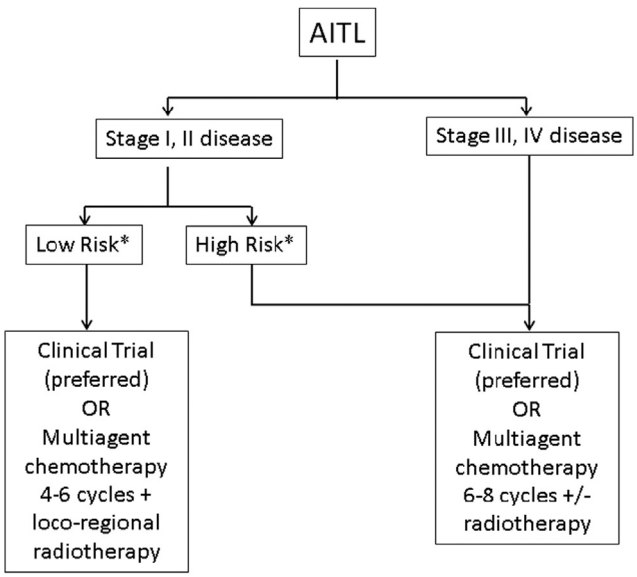

Figure 4. Proposed algorithm for initial management of AITL.

response rate was 30% at 4 years for chemo-sensitive patients and 23% at 4 years for chemo-resistant patients.[57] Based on these findings, allogeneic stem cell transplantation (alloSCT) was tried for the possibility of a cure in AITL patients who had received two or more lines of chemotherapy or who had failed ASCT. The 3-year OS in this study was 64%, but it was associated with a non-relapse mortality rate of 25% at 1 year, which was higher in the group of patients with poor performance status.[60] As in patients undergoing ASCT, chemo-sensitive patients had statistically significantly better outcomes than those with chemo-refractory disease in patients undergoing alloSCT.[57,60] It is possible that results of these studies may be biased because of age and/or comorbidity criteria used for transplant.[57,59]

CONCLUSION

AITL is a subtype of PTCL associated with typical clinical, laboratory, and pathologic features. Our understanding of the biology thus far has highlighted the role of neoplastic T cells and its interaction with the cells present in the surrounding tumor microenvironment. First-line therapy and newer combination regimens have not shown a significant improvement in OS rates, suggesting knowledge gaps in our complete understanding of the disease. Strategies targeting the NF-κB pathway and monocolonal antibody against CD52 antigen have shown promise. Larger studies are needed to address their role in maintaining sustained effects. We propose an algorithm for the initial management of AITL (Figure 4).

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