Angioimmunoblastic T-Cell Lymphoma: Clinical Aspects and Recent Advances in Biology and Therapy

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Abstract: Angioimmunoblastic T-cell lymphoma (AITL) comprehends 20% of the peripheral T-cell lymphomas (PTCL). Although rare, its clinical features may overlap with many other inflammatory, infectious or neoplastic disorders. Therefore, that patients are often diagnosed with advanced stage disease, which contributes for the disease´s dismal prognosis. The clinical presentation of AITL is frequently an assemblage of symptoms including generalized and painful lymphadenopathy, multiple cutaneous alterations, hypergammaglobulinemia, fever, loss of weight and significant autoimmune phenomena. Recent advances in AITL biology have implicated a cell with T-follicular helper phenotype as the origin of the disorder. This rare type of T lymphocyte has a peculiar capacity of interact with microenviroment, which results in an important production of cytokines, explaining the clinical findings of this type of lymphoma. In addition to its pathologic features, AITL can be distinguished from other T-cell lymphomas based on gene expression arrangement, suggesting that AITL has a unique biology. Moreover, somatic mutations in the epigenetic regulators DNMT3A, TET2, IDH2, and, especially, in the multifunctional RHOA GTPase gene, have emerged as very consistent genetic abnormalities in AITL. Considering its low incidence, the development of clinical trials in AITL is a challenging matter. Furthermore, the majority of data available originates from studies that contain other subtypes of PTCL, making prognosis analysis and treatment decision a tough work. In this review, we discuss the biological and clinical aspects of AITL and the alternatives for frontline treatment and the management of relapsed disease.

Keywords: Angioimmunoblastic T-cell lymphoma, T-follicular helper cells, gene expression profiling, TET2 mutation, RHOA GTPase mutation, relapsed disease.

1. INTRODUCTION

Angioimmunoblastic T-cell lymphoma (AITL) was firstly reported in 1974 [1]. It is an uncommon lymphoid malignancy, accounting for approximately 2% of all non-Hodgkin lymphomas. According to a recent survey, AITL corresponds to 15-20% of the heterogeneous groups of peripheral T-cell lymphomas (PTCL). [2] Interestingly, the disease is more common in Europe than in North America or Asia, where its prevalence is estimated at 16% and 18%. In addition, its incidence is 0.05 new cases per 100,000 people in the US [2,3]. Yet, no etiological agents or ethnical predisposition have been identified. Commonly, AITL tends to affect middle aged and elderly population without sex predilection. Based on Surveillance, Epidemiology, and End Results (SEER), none survival improvement has been shown for AITL patients over the past two decades [4, 5].

The clinical presentation of AITL is frequently an assemblage of symptoms [6]. Typical clinical presentation is illustrated by constitutive symptoms, such as weight loss, fatigue, and fever. Usual manifestations also involve pruritic skin rash, hepatosplenomegaly, and generalized lympha-denopathy [5-7]. Hematological features may include autoimmune hemolytic anemia, thrombocytopenia and polyclonal hypergammaglobulinemia [8,9]. Furthermore, bone marrow involvement is reported in up to 70% of the cases and it tends to correlate with B symptoms, hepatosplenomegaly, abnormal laboratory findings, and higher levels of circulating tumor cells [10]. Overall, AITL overlaps many other reactive and neoplastic disorders, and patients often present with advanced disease due to delay in accurate diagnosis.

AILT usually preserves some of the functional characteristics of non-neoplastic T-cells, such as cytokine production and immune system stimulation. Non-specific immune cell activation in AITL is associated with a paradoxical combination of immune hyperactivity and immunosuppression [11]. Actually, AITL exhibits a complex network of interactions between the neoplastic T-cells and the rich microenvironment, presumably mediated by the neoplastic T-cells with T-follicular helper (TFH) cells properties [12]. As a result, patients are susceptible to systemic inflammation and

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opportunistic infections, which appear to be the major cause of morbidity and mortality.

More recently, both genetic profiling of PTCL and the discovery of specific mutations in AITL has led to a better understanding of this relatively rare disease. Here we will review some clinical aspects and discuss recent advances in molecular diagnosis and treatment of angioimmunoblastic T-cell lymphoma.

2. AITL MORPHOLOGY AND IMMUNOPHENOTYPE

2.1. Lymph Node Involvement

In general, AITL presents with diffuse lymph node involvement, including atypical clear cell components, abundant follicular dendritic cell (FDC) hyperplasia, and complex arborescent vascular structures [13]. In addition, neoplastic TFH cells appear isolated or in sheets, along with a great number of non-neoplastic B and T-cells, histiocytes, plasmocytes, neutrophils and eosinophils. All these components may be present in different degrees, forming a wide variety of morphologic patterns [14].

Typically, AITL has been classified into three histologic subtypes, based on patterns of lymph node involvement. It ranges from modest infiltration in the paracortical areas to an ample diffuse involvement. The morphologic limits of each pattern are arbitrary. Generally, more than one histologic subtype is found in the same specimen, highlighting the idea that those subtypes form a continuum spectrum of the disease evolution [14, 20].

In pattern I, found in 10-20% of the cases, the follicular structure of the lymph node is partially preserved. Some follicles can be hyperplastic, with prominent germinal centers. The neoplastic proliferation is found in the interfollicular area, which is extremely polymorphic and can be difficult to detect. In pattern II, found in up to 50% of the cases, the lymph node appears predominantly affected by cell proliferation, with small residual follicles, anomalous arrangements and partial destruction. The follicular centers are atrophic, most of the times sclerotic with a clear paracortical expansion. In pattern III, the lymph node shows a diffuse involvement. The follicles are scarce, and can be absent. When present, they are atrophic, mainly composed by follicular dendritic cells with lymphatic population depletion [21].

In patterns II and III, the cellular population tends to be monotonous, and in some cases can show numerous atypical lymphoid cells. The TFH cells usually vary from small to medium size, with round hyperchromatic nuclei. Their cytoplasm is mostly clear and makes the cell limits evident. In addition, TFH cells can accumulate around the arborescent venules or form nodules or masses of neoplastic cells [22].

Extension to perinodal adipose tissue is commonly found and usually followed by vascular and dendritic cells proliferation. Curiously, the extranodal extension tends to spare the subcapsular sinuses, which can be filled with monocytes or histiocytes B-cells. The lack of neoplastic involvement in subcapsular sinuses is a useful morphologic finding to corroborate the diagnosis [5,6].

The discovery that AITL relates to TFH lymphocytes was a milestone in the understanding of the disease biology. TFH cells comprise a very rare type of T-cells localized in the germinal center. These cells display an intimate interaction with B-cells and FDCs [15-17]. It seems that the overrepresentation of these two subsets of cells is a consequence of the typical TFH dysregulation seen in AITL. In a normal scenario, all the mentioned cell types exchange trophic signals to each other, whereas in AITL the malignant clone abnormally employs the traffic of growing signaling among these cells to its own advantage [18].

Other components of the tumor appear to contribute to the lymphoma-associated pro-inflammatory microenvironment of AITL [19]. Some of those relevant factors are interleukin-17-producing (Th17) T-cells and mast cells (MCs). As previously shown, MCs directly synthesized interleukin-6 and thus contribute to the establishment of a pro-inflammatory, Th17 permissive environment in AITL. In addition, Th-17 cells are central in the pathogenesis of autoimmune disturbances such as the ones observed in AITL. In parallel to the Th-17 expansion, other cytokines produced by different cell subsets have been long implicating in AITL, such as TNF, IL-1, IL-4 and interferon-gama [8].

Besides the miscellany of inflammatory cells, we must highlight that some of them can show peculiar aspects, specially the immunoblasts. These lymphocytes can show B, T or null immunopheno type, presenting with irregular and lobulated nucleus, and evident nucleolus, much similar to the Reed-Sternberg cells [23]. Some cases show a rich plasmocytes population, frequently found around the arborescent blood vessels [24]. The proliferation of postcapillary venules – which happen in all morphologic patterns – is

probably derived from the oversecretion of the vascular endothelial growth factor (VEGF) by neoplastic and endothelial cells [25].

In some cases, mainly during initial stages, the neoplastic cells may be found in the lymphoid follicles and parafollicles adjacent areas. Such findings, despite being hard to define without immunohistochemistry, contribute to the idea that the neoplasm originates from the cells of the follicular center [22, 26].

2.2. Immunophenotype

Neoplastic TFH cells commonly express pan-T markers, such as CD2, CD3, CD5 and CD45RO, besides CD4. Considering that those cells are constituents of follicular centers, they may express markers more commonly observed in B-cells from follicular centers, such as CD10 and BCL-6. The CXCL-13 expression from TFH cells is very useful in its detection and, consequently, in the AITL diagnosis. CXCL-13 stimulates the expansion of FDCs, promotes the attraction of B-cells to follicular centers, and supports the development and activation of those B-cells [27].

The small lymphocytes in the microenvironment express pan-B and Pan-T markers in their specific subpopulations. Those T-cells show a proportional distribution between CD4 and CD8. Frequently, the immunoblasts are activated B-cells, that express CD30 and, in many cases, EBV [28]. The FDCs usually express CD21, CD23 and CD35. Detection of FDCs in extra follicular areas can be useful to diagnosis confirmation [26, 28].

Notably, TFH cells do not usually show EBV markers. Non-neoplastic cells, mainly B-cells, do show in about 75% of cases [29]. Until now, there are many discussions whether EBV infection can be the cause of neoplastic transformation or it is the consequence of patient immunosuppression [5,30]. Currently, it is more commonly believed that EBV infection is an opportunistic phenomenon due to the host's immunologic imbalance. To support that idea, there have been described AITL in patients who did not show signs of EBV infection and afterwards, with the evolution or disease relapse, infected cells started to be observed [29,31].

In about 10% of cases monoclonality cannot be proved and some patients show an indolent clinical course. For some authors, the evidence of the presence of pre-neoplastic or dysplastic lesion has not been completely accepted, as suggested in the original description of the disease [32, 33].

3. AITL GENE EXPRESSION PROFILING (GEP) AND SPECIFIC MUTATIONS

AITL can be distinguished from other T-cell lymphomas based on gene expression arrangement, suggesting that AITL has a unique biology. In a well-designed GEP study that compared series of AITL and PTCL-not otherwise specified (PTCL-NOS), 678 genes were useful in distinguish AITL (442 over expressed genes) and PTCL (236 over expressed genes) [18]. The genes of the AITL signature belonged to several functional categories. The most significant overrepresented gene ontology subgroups in AITL were related to cell-to-cell communication and adhesion, immune response, vascular biology, and extracellular matrix. Compared to PTCL, AITL had higher levels of expression of cell adhesion molecules (cadherins, integrins, CD151), membrane receptors (CD10, CD40 ligand, CD200, PDCD1), and proteins involved in membrane signaling. Furthermore, AITL was also characterized by an overrepresentation of B-cell, plasma cell-related genes, and FDCs, as well as complement factors, extracellular matrix components (laminin, collagen, ladinin, fibronectin), and factors and enzymes involved in matrix synthesis and remodeling (TGF-β, fibroblast growth factor, matrix metalloproteinases). Several genes related to vascular biology, including vascular growth factors, endothelium-related genes and coagulation factors, were also over expressed in AITL.

In another study, GEP was performed on pretreatment biopsy specimens from 372 newly diagnosed patients, including 114 AITL, 31 ALK-positive, and 48 ALK-negative anaplastic large cell lymphoma (ALCL), 14 adult T-cell lymphoma and 44 extranodal NK/T-cell lymphoma that were further separated into NK-cell and gdT-cell lymphomas [34]. A molecular signature of AITL unique genes – including those involved in cell morphology and migration, intracellular signaling, vascularization, and cell cycle – predicted 77% of the pathologically diagnosed AITL as such, whereas 21 of 150 (14%) pathologically diagnosed PTCL-NOS cases were reclassified as AITL. Interesting, after merging highly correlated signatures [35], four distinct genetic functional scores with biological plausibility were molded for AITL: B-cell signature, monocytic signature, cytotoxic signature associated with CD8+ T-cells, and p53-induced target

gene signature. Both in the training setting and in the validation set the B-cell-associated signature predicted a favorable outcome, whereas the other three were associated with poorer outcome.

A large accuracy study conducted by the European T-Cell Lymphoma Study Group and the International Peripheral T-Cell Lymphoma Project showed that molecular profiling could improve classification and prognostication of nodal peripheral t-cell lymphomas [36]. In 244 PTCL cases, including 158 PTCL-NOS, 63 AITL, and 23 ALK-negative ALCL, a GEP-based classification allowed the identification of specific molecular signatures, as well as a better difference among survival curves. The overall accuracy of the molecular classifier was quite high: 98% to 77% for AITL and 98% to 93% for ALK-negative ALCL in test and validation sets of patient cases, respectively. In addition, the molecular classifier discriminated some TFH PTCL-NOS from AITL, providing further evidence that a group of PTCL-NOS shares a TFH derivation but is distinct from AITL.

More recently, specific mutations in AITL have been further explored offering relevant insights into its pathogenesis. Many genes involved in angiogenesis, especially VEGF, are over expressed in the typical signature of AITL, as expected. For some time it was assumed that this signature had more to do with the microenvironment than with the malignant clone itself. However, recent data has challenged this view, demonstrating that clonal T-cells are able to maintain a paracrine or autocrine circuit by producing VEGF and VEGFR [37].

Somatic mutations in the epigenetic regulators DNMT3A, TET2, IDH2, and, especially, in the multifunctional RHOA GTP ase gene, emerged as very consistent genetic abnormalities in AITL. Both TET2 and IDH2 mutations are common events in myeloid malignancies, but much less frequent in lymphoid ones [38]. Curiously, in AITL, there are series that identified a high rate of mutation in both genes [39, 40]. As much as 76% of AITL cases could harbor TET2 or IDH2 mutations. It is interesting to note that even in cases with clinical presentation of PTCL, the finding of TET2 or/and IDH2 mutation were strongly correlated to TFH phenotype. Now, it is conceivable that all these T-cell lymphomas bearing TET2/IDH2 and TFH phenotype may be part of a very similar pathological entity. Mutations in DNMT3A were reported in 11-33% of AITL cases. All these cases, in these studies, also displayed TET2 mutation [41, 42].

According to recent reports, RHOA GTP ase gene is also mutated in more than two-thirds of AITL cases [43]. A very constant hot spot encoding p.Gly17Val was the only abnormality found in RHOA gene. The Gly17Val modifies a GTP binding site, preventing the activation of the protein and inhibiting the RHOA wild-type allele. A very detailed study on RHOA mutation in T-cell neoplasms revealed that all cases with p.Gly17Val had TET2 mutations as well [44]. Epigenetic modifications caused by TET2 (and maybe IDH2 and DNMT3A) precede RHOA mutation in the oncogenetic pathway. There are two lines of evidence to support this relevant observation. First, differently to TET2 mutations that can be identified both in tumor and in micro environmental cells, the RHOA mutation was exclusively detected in tumor cells. Second, in some cases, the malignant clone presents TET2 loss-of-function mutations but not the RHOA Gly17Val mutation. It is noteworthy that in the 170 cases of hematologic malignancies studied by Sakata-Yanagimoto *et al*. only AITL and PTCL presented mutations in RHOA. Interestingly, all the 17% of cases of PTCL with RHOA mutations had AITL phenotype. This suggests that RHOA is an exclusive molecular event of AITL. Obviously, this observation opens a large avenue of opportunities for targeted therapies in this fatal type of lymphoma.

4. PRIMARY TREATMENT OF AITL

Considering its low incidence, the development of clinical trials in AITL is a challenging matter. Furthermore, the majority of data available originates from studies that contain other subtypes of PTCL, making prognosis analysis and treatment decision a tough work.

As previously confirmed, the International Prognostic Index (IPI) was not able to distinguish different subgroups in AITL and its application is highly criticized. [6] Actually, two relevant retrospective studies have been taken into consideration in order to discuss prognostic data in AITL. [45,46] The International T-Cell Project enrolled 1,314 patients, including 213 AITL cases. In that study, patients with low IPI had a 5-year disease-free survival rate of 33% [6, 45]. However, in the same population, the application of the Prognostic Index for AITL (PIT) was able to distinguish two different prognostic subgroups: low risk (0-1 risk factor) and high risk (2-5 risk factor) with a 5-year overall survival rate of 44% and 24%, respectively [6].

Systemic chemotherapy is considered the standard first-line treatment for AITL, and once the therapeutic plan has been defined, two aspects should be highlighted: (1) the prognostic score cannot be the main factor influencing the initial treatment and; (2) anthracycline-based regimens produce low response rates in the long term. The limitations of this approach are usually due to comorbidities of elderly patients and the risk of disseminated infection, which is the main cause of mortality.

The combination of cyclophosphamide, vincristine, doxorubicin, and prednisone (CHOP) induces response in 50% of patients, despite high rates of relapse. In general, relapses occur regardless of clinical condition [47]. Observation or prednisone alone is rarely indicated, despite the reports of asymptomatic disease or spontaneous regression [48].

As previously shown, there is no difference in terms of overall survival regarding the use of ACVBP (doxorubicin, cyclophosphamide, vindesine, bleomycin and prednisone), CHOP or mBACOD (methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine and dexamethasone) [47, 48].

As an alternative to CHOP, the German High-Grade Non-Hodgkin Lymphoma Study Group studied the combination of that regimen to etoposide. That trial enrolled 343 patients, including 28 AITL cases. As a result, patients younger than 60 years old and presenting with normal LDH benefited from the combination with etoposide, showing a 3-year event-free survival rate of 75.4% versus 51% in other subgroups [49]. Additionally, patients older than 60 treated with CHOP had a similar survival outcome to CHOEP, suggesting that the combination must be used for patients with a better performance status and prognosis.

First-line therapy with auto logous bone marrow transplant (BMT) in patients with chemo sensitive disease has been explored in phase 2 trials [47, 48, 50, 51]. The Nordic study, which included 30 AITL patients, showed 52% and 49% for 5-year overall survival and disease-free survival, respectively. In this trial, patients were treated with CHOEP (CHOP for people over than 60) and consolidation with BEAM protocol [50]. Due to those results, several guidelines have recommended auto logous BMT as a consolidation treatment for patients with chemosensitive disease after first-line chemotherapy in AITL.

Other treatment proposals include the use of low-dose methotrexate and steroids, fludarabine, and gemcitabine. However, the small number of patients involved in those trials does not permit any comparison between regimens [52-54].

Monoclonal antibodies such as rituximab have been tested in first-line scenario trials. The Groupe d'Etude des Lymphomes de l'Adulte (GELA) recently published a phase 2 trial involving 25 patients treated with CHOP in combination with rituximab [55]. A complete response rate of 44% was observed. With a median follow-up of 24 months, the 2-year progression-free survival rate was 42% and overall survival rate was 62%. Interestingly, the presence of EBV DNA in peripheral blood mononuclear cells (14/21 patients) correlated with Epstein-Barr virus score in lymph nodes and the detection of circulating tumor cells. Despite peripheral EBV clearance after treatment, the viral load at diagnosis (>100 copy/μg DNA) was associated with shorter progression-free survival.

Alemtuzumab, a monoclonal antibody that targets CD52, has been studied in combination with CHOP as well. This combination was able to reach a complete response rate ranging from 65% to 71% [56, 57]. However, authors describe high rates of opportunistic infections, such as JC virus encephalitis, invasive aspergillosis, pneumocystosis, sepsis, and cytomegalovirus reactivation. Currently, other ongoing trials should better define the role of alemtuzumab in combination with first-line chemotherapy regimens.

5. TREATMENT OF RECURRENT AITL AND PERSPECTIVES

Candidates to hematopoietic bone marrow transplant must be treated with second-line chemotherapy before transplantation. Consolidation regimens with high-dose chemotherapy and autologous stem cell rescue (HDT/ASCR) or allogeneic BMT might be recommended to those with complete response or partial response. [58, 63-64] Bulky disease areas can be treated with radiation therapy before or after the high-dose therapy. Patients who are not eligible to intensive treatment must be treated with second-line regimen or palliative radiation therapy. [47-48, 60] Unfortunately, no randomized controlled trial has been developed in order to better select the second-line option for those refractory patients.

Some retrospective studies evaluate the role of HDT/ASCR in patients with relapsed and refractory

PTCL. [58-60] In patients with relapsed or primarily refractory PTCL (N=36) submitted to HDT/ASCR, the 3-year event-free survival and overall survival were about 37% and 48%, respectively. Those survival outcomes are similar in patients with relapsed diffuse large B-cell lymphoma (DLBCL) that received HDT/ASCR in a retrospective analysis (42% and 53%, respectively) [58]. In another retrospective study, conducted in patients with relapsed or refractory PTCL (n = 24; patients with ALK-positive ALCL were excluded), who received HDT/ASCR, the progession-free survival and the overall survival rates in 5 years were 24% and 33%, respectively. These results were also similar to the ones observed in patients with relapsed DLBCL (34% and 39%, respectively) [59]. Aggressive second-line chemotherapy with ifosfamide, carboplatin, etoposide (ICE), followed by HDT/ASCR, was assessed in patients with relapsed/refractory PTCL [60]. Among 40 patients treated with ICE, 27 (68%) were submitted to HDT/ASCR. The median progression-free survival was about 6 months from the last cycle of ICE. Seventy per cent of responders relapsed within a year. However, patients with relapsed disease had a 3-year progession-free survival significantly higher than those who were primarily refractory (20% versus 6%). Based on current data, salvage therapy for patients with relapsed/refractory PTCL remains unsatisfactory, even with the incorporation of HDT/ASCR.

A retrospective analysis of patients with PTCL who were submitted to HDT/ASCR at Stanford University (n = 53), the 5-year progression-free survival for patients who experimented first-line complete response/partial response (CR/PR), second-line CR/PR, and those with refractory disease was 51%, 12%, and 0%, respectively. The 5-year overall survival was 76%, 40% and 30%, respectively [61]. The most relevant prognostic factors were the level of response and the number of previous regimens received before the transplant.

Recent reports have shown that allogeneic BMT can be an option for patients with relapsed/refractory PTCL. In a retrospective analysis from the French Registry of patients who received allogeneic BMT (N = 77; PTCL-NOS 35%; ALCL 35%; AITL 14%), 5-year event-free survival and overall survival were 53% and 57%, respectively [62]. The transplant-related mortality (TRM) rate was 34% and TRM at 100 days was 21%.

In a recent analysis of the M.D. Anderson Cancer Center, results have been reported for patients with T-cell lymphomas (N = 196; PTCL-NOS, n = 61; ALCL, n = 50; AITL, n = 19) who were submitted to HDT/ASCR (n = 119) or allogeneic BMT (n = 77; myeloablative conditioning in 75%) [63]. Among the patients who underwent HDT/ASCR, progression-free survival and overall survival were 30% and 39%, respectively, after a median follow-up of 39 months. Among the patients who underwent allogeneic BMT, progression-free survival and overall survival were 30% and 43%, respectively, after a median follow-up of 65 months. In patients diagnosed with nodal T-cell lymphoma (PTCL-NOS, ALCL, or AITL), 3-year progression-free and overall survival were 23% and 38%, respectively. Patients in this subgroup were primarily (97%) transplanted in a context of rescue.

Other studies have evaluated the role of allogeneic BMT using reduced intensity conditioning (RIC) in patients with relapsed/refractory PTCL. A retrospective study of the European Society for Blood and Marrow Transplantation database showed that allogeneic BMT induced longer remissions in patients with AITL (n = 45, 62% of patients had undergone more than two lines of treatment previous to the transplant) [64]. Myeloablative conditioning was used in 56% of patients, whereas the other portion received RIC. The cumulative rate of 1-year non-relapse mortality was 25%. These rates were the same in the myeloablative conditioning (29%) and RIC (24%). The estimated rate of 3-year relapse was 20%. 3-year progression-free survival and overall survival were 54% and 64%, respectively. The results were not significantly different when comparing the two regimen of conditioning. Patients with chemosensitive disease had a significantly better progression-free survival, when compared to refractory disease (66% versus 33%, respectively).

Other options to patients with relapsed/refractory PTCL, not eligible to high-intensity chemotherapy, have been tested in the last years. In a pilot study, standard-dose alemtuzumab produced an overall response rate of 36% (21% complete response) in patients with relapsed/refractory PTCL (n = 14). CMV reactivation was observed in 42% of patients [65].

In September 2009, pralatrexate became the first FDA-approved single agent to treating patients with relapsed/refractory PTCL. Pralatrexate is a new antifolate drug with high affinity for reduced folate carrier type 1 (RFC-1). It has shown a significant activity in patients with relapsed/refractory T-cell lymphoma [66-68]. Results of a phase II study

(PROPEL) showed overall response rate of 29% (11% complete response) in patients previously treated with relapsed/refractory PTCL (n = 109) [67]. The patients in this study had received an average of three previous systemic therapies (range, 1-12). Moreover, 63% were refractory to the most recent line of treatment, 24% had never responded to any treatment and 16% were previously submitted to autologous BMT. The average duration of response was 10 months. Progression-free survival and overall survival were 3.5 months and 14.5 months, respectively [67].

Romidepsin is a histone deacetylase inhibitor that was tested as a single agent in a phase II multicentric study for patients with relapsed/refractory PTCL (n = 130) [69, 70]. Patients in this trial were submitted on average to two systemic therapies (range, 1-8) and 16% failed to a previous auto logous BMT. Overall response rate was 25% (15% complete response) [70]. The median response duration was 17 months. Median progression-free survival to all patients was four months and to those patients with complete response was 18 months.

Bendamustine is an alkylating agent with a purine-like benzimidazole ring component, which was recently evaluated in a phase II multicentric study (BENTLEY trial) in patients with relapsed/refractory PTCL (n = 60; AITL, 53%; PTCL-NOS, 38%) [71]. The patients received on average one previous treatment (range, 1-3) and 45% were considered refractory to the last line of treatment. The majority of patients received CHOP or CHOP-like treatment (92%). Overall response rate after three cycles of bendamustine was 50% with complete response in 28% of cases. Forty patients (67%) completed three or more cycles of bendamustine and 25% received all 6 cycles of therapy. The median duration of response was about 3.5 months. Progression-free survival and overall survival for all patients were 3.6 months and 6.3 months, respectively.

Additionally, data of a phase II trial in patients with non-Hodgkin lymphoma with CD30 expression showed that brentuximab vedotin resulted in 54% and 33% overall response rates in patients with AITL (n = 13) and PTCL-NOS (n = 21), respectively [72].

6. CONCLUSION

Angioimmunoblastic T-cell lymphoma represents a distinct clinicopathological entity among nodal peripheral T-cell lymphomas, usually with a dismal prognosis. Typical clinical findings are constitutive symptoms, such as weight loss, fatigue, and fever. Furthermore, common manifestations also involve pruritic skin rash, hepatosplenomegaly, and generalized lymphadenopathy. Because of immune dysregulation and cytokine production, patients are susceptible to systemic inflammation and opportunistic infections, which appear to be the major cause of death.

Typically, morphological classification defines three different patterns of nodal involvement, as a continuum that ranges from modest infiltration in the paracortical areas to an ample diffuse effacement. Recent data concerning the identity of the normal cellular counterpart of AITL are emerging, and it is now believed that AITL derives from a follicular helper T-cell subset. These cells display an intimate interaction with B-cells and follicular dendritic cells, and it seems that the overrepresentation of these two subsets of cells is a consequence of the typical follicular helper T-cell dysregulation seen in AITL.

In the last years, genetic profiling of AITL has shed more light into the biology of this rare disease, pointing out to differences in outcome survival and other prognostic data. Moreover, genomic sequencing of AITL has revealed the presence of acquired mutations in genes never related to this type of tumor before, as TET2, IDH2, and RHOA GTPase mutations. Given the poor outcome of AITL and the scarcity of effective treatment regimens, we believe that collaborative efforts should be done in order to develop prospective clinical trials. Those studies should help the scientific community to better understand the biological behavior of AITL so that specific targeted therapies can be adequately developed.

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