Chapter 9
Adult T-Cell Leukemia/Lymphoma

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Introduction

Adult T-cell leukemia/lymphoma (ATLL) is a mature peripheral T-cell neoplasm caused by human T-cell leukemia virus type 1 (HTLV-1). The clinical entity was proposed by Takatsuki et al. in 1977 [1], with HTLV-1 discovered as the causative virus in 1980 by Poiesz et al. [2]. Beyond ATLL, HTLV-1 is associated with several entities, including HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP), infective dermatitis, and severe forms of parasitic infections (disseminated strongyloidiasis, crusted scabies) [3, 4]. ATLL carries a dismal prognosis and is essentially incurable by conventional drugs. The largest updated retrospective Japanese study published by Katsuya et al. included 1594 patients treated with modern aggressive therapies, with reported median survival (MS) of 8.3 and 10.6 months for acute and lymphomatous types, respectively [5]. Only allogeneic hematopoietic stem cell transplantation (HSCT) appeared to be curative in a group of patients who are eligible for this approach [6–8]. This chapter will review the epidemiology, clinical manifestations, diagnostic considerations, and conventional and novel treatment approaches, including ongoing clinical trials and preclinical agents.

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Epidemiology

ATLL geographic distribution is primarily driven by HTLV-1 epidemiology. HTLV-1 prevalence has been estimated at ten million individuals worldwide and is most endemic in southwestern Japan, the Caribbean Basin, Central and South America, and western Africa (Fig. 9.1) [3, 9, 10]. In the western world, the highest prevalence of HTLV-1 infection is found in Haiti, Jamaica, Dominican Republic, northeastern Brazil, and Peru [3]. In the United States, cases of HTLV-1 and ATLL are seen as an effect of migration, particularly from West Africa and the Caribbean (Fig. 9.1). South Florida is the continental region most proximal to the Caribbean; therefore HTLV-1-associated diseases are commonly encountered in Miami [11–13]. Large metropolitan regions along the Eastern Seaboard also have significant populations with HTLV-1, particularly Boston and New York [11, 14]. Boston, in particular, has a large population of Cape Verdean immigrants, who are likely at risk for HTLV-1 infection, but few data exist. HTLV-1 has rarely been described in the US-born population [13].

The virus is primarily transmitted via breastfeeding. The risk of infection in children of seropositive mothers correlates with the viral load in breast milk, the concordance of HLA class I type between mother and child, and the duration of breastfeeding [15, 16]. In Japan, screening of pregnant women and avoiding breastfeeding in those infected has reduced transmission by 80% [17, 18]. Other modes of transmission include blood transfusion, sharing of needles, and sexual intercourse [3, 11]. Most people infected with HTLV-1 remain asymptomatic throughout life, and it is difficult to determine which individuals will develop symptomatic HTLV-1-associated disease [19, 20]. Among HTLV-1 carriers, the general lifetime risk of developing any HTLV-1-associated disease, including ATLL, HAM/TSP, uveitis, polymyositis, and arthropathy, may be close to 10% [21–24].

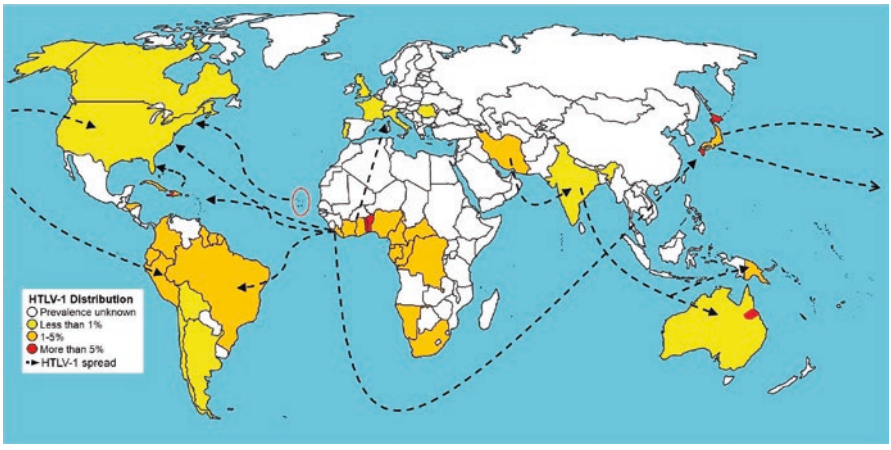


Fig. 9.1 Geographic distribution and spread of HTLV-1

ATLL is associated with some intriguing characteristics. First, ATLL seems to be hyperendemic in southwestern Japan, particularly the Kyushu region [25]. Second, HTLV-1 establishes a lifelong latent infection in human CD4+ T-cells. ATLL, in particular, has a very long latency period, and only patients infected with HTLV-1 early in life (via breastfeeding) are generally at risk. Those individuals infected later in life via blood transfusions, intravenous drug use, or sexual contact are more at risk for HAM/TSP and other HTLV-1-associated illnesses [26]. Malignant transformation leading to ATLL develops in HTLV-1-infected individuals with a cumulative lifetime risk of 4–7% [27]. Third, ATLL occurs predominantly in adults between the sixth and seventh decades in Japan [27, 28] and fourth to fifth decades in the Caribbean Basin and Central and South America [25, 29, 30]. Unfortunately, there is no clear evidence on why this regional discrepancy exists.

The viral oncogenic protein Tax is responsible for transforming the CD4+ T-cell into a cancerous ATLL cell [26, 31]. Infection of T lymphocytes with HTLV-1 results in an increase in proviral loads, with a more pronounced effect for HTLV-1 proviral DNA load. An antibody response against Gag and Env (viral proteins) and Tax-specific cytotoxic T-cell responses induces killing of infected cells. HTLV-1 can evade the immune response by reducing Tax and stimulating HBZ (basic leucine zipper factor) expression. HBZ would subsequently promote the establishment of a chronic infection by inhibiting Tax-dependent viral transcription, stimulating its own expression, and inducing T-cell proliferation [31]. Tax protein expression is undetectable in circulating ATLL cells; HBZ is the only viral protein consistently expressed in ATLL [26, 31].

Clinical Features

Clinically, ATLL is classified into four subtypes, namely, acute, lymphomatous, chronic, and smoldering, as defined by the Shimoyama criteria [32]. The acute and lymphomatous forms are by far the most common subtypes and are often grouped as "aggressive ATLL." The acute subtype presents with a leukemic phase consisting of circulating atypical lymphocytes (ATLL cells) known as "flower cells" (Fig. 9.2), profoundly increased calcium level, and high serum lactate dehydrogenase (LDH). Additionally, the acute type will often present with diffuse lymphadenopathy (LAD) and organ infiltration. The lymphomatous subtype presents with extensive (often bulky) lymphadenopathy, markedly elevated LDH, organ infiltration, and, by definition, an absence of circulating ATLL cells in the peripheral blood (<1%). The smoldering and chronic forms present with circulating ATLL cells (absolute lymphocyte count $<4\times10^3$ cells/μL or $\geq4\times10^3$ cells/μL, respectively), normal or mildly elevated LDH (<1.5 or <2 times the upper limit of normal, ULN, respectively), and involvement of the lung, skin, or liver (in chronic only), but no other extranodal sites, and no hypercalcemia. The chronic subtype is further divided into unfavorable and favorable, based on the presence or absence of risk factors such as elevated LDH level greater than the ULN, serum blood urea nitrogen level greater than the ULN,

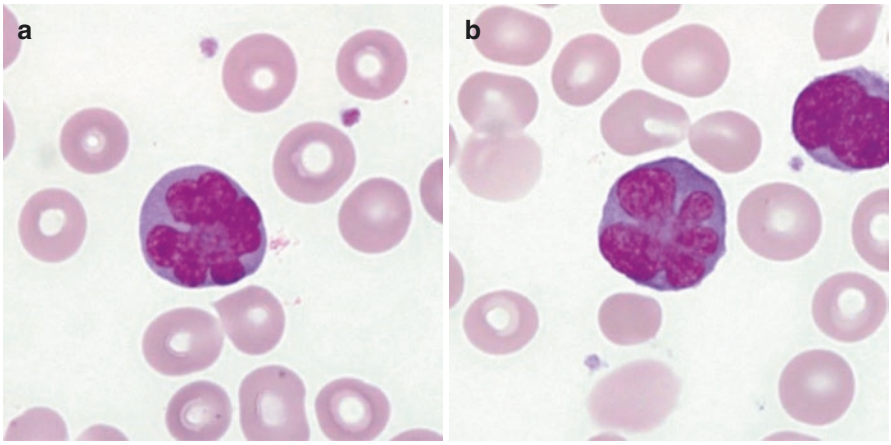


Fig. 9.2 (**a**, **b**) Flower cells (atypical lymphocytes). (Photos courtesy of UNC Hematopathology)

and serum albumin level lower than the normal lower limit [32]. In summary, the smoldering, chronic, and acute subtypes of ATLL can be viewed on a continuum of leukemic involvement, with the smoldering subtype representing the mildest form of the disease. The acute and lymphomatous subtypes represent the most aggressive forms of the disease, with risk for tumor lysis syndrome (TLS) and central nervous system (CNS) involvement. All subtypes of ATLL have variable dermatologic manifestations.

Comorbid opportunistic infections are often seen in ATLL patients as a result of immunosuppression caused by dysfunctional HTLV-1-infected T-cells. Parasitic (especially strongyloidiasis), fungal, and viral infections are frequently associated with all forms of ATLL [3, 30, 33, 34]. Because of the risk of severe infection in patients with ATLL, prophylaxis against these infectious complications is paramount.

Diagnosis and Pertinent Workup

The diagnosis of ATLL involves a comprehensive history which will include epidemiologic, clinical, and laboratory/pathologic data. Although almost all patients diagnosed with ATLL were born in HTLV-1 endemic areas, there are rare cases where the patient was born in a non-endemic region [13]. Clinically, hypercalcemia is an important marker; it occurs in up to 70% of patients with ATLL during the entire course of their disease and is often accompanied by lytic lesions [35]. Hypercalcemia is most associated with the acute-type ATLL; the indolent subtypes would only develop hypercalcemia on progression to an aggressive type. A parathyroid hormone-related peptide is frequently increased in ATLL patients [35, 36].

Severe eosinophilia has been described in ATLL patients [37]; however, most recent data relate this finding to dysregulation of an appropriate Th2 response against opportunistic pathogens. Conversely, patients with disseminated strongyloidiasis may present with eosinopenia [3, 38, 39]. In the leukemic phase, the white blood cell count may increase into the hundreds of thousands, and the peripheral blood smear may have "flower cells" which are pathognomonic for ATLL. Any suspicion must still be confirmed by HTLV-1 testing. Confirmation of infection is generally performed by enzyme-linked immunosorbent assay (ELISA) and should always be confirmed by Western blot and/or polymerase chain reaction (PCR) [25–27, 32]. Although a positive test does not confirm ATLL, a negative test does rule out ATLL.

The predominant immunological phenotype of neoplastic cells is that of a CD4+ helper T-cell: CD3+, CD4+, CD7−, CD8−, and CD25+ [40]. CD30 expression is variable in ATLL, with a lower percentage of CD30+ cells in the acute than in the lymphomatous ATLL subtype (positive in 28% and 47%, respectively) [41]. Lymphomatous presentations depend on an excisional lymph node biopsy for diagnosis, which should have flow cytometry and immunohistochemical (IHC) testing. Additional IHC tests include anaplastic lymphoma kinase (ALK), paired box 5 (PAX5), and terminal deoxynucleotidyl transferase (TdT) which are all negative in ATLL. The Ki-67 proliferation index is very high in aggressive ATLL [40]. Bone marrow aspiration and biopsy may be performed to obtain a diagnosis or to complete staging and have prognostic relevance [42].

In clinical practice, evaluation of ATLL patients should always include a complete cell blood count with differential and peripheral blood smear; additionally, all patients with ATLL should have an LDH, a TLS panel, including uric acid, phosphate, calcium, potassium, and creatinine levels, and a soluble interleukin 2 (IL-2) receptor test. Glucose-6-phosphate dehydrogenase (G6PD) testing should also be sent with the initial work-up in order to evaluate for the presence of a hereditary deficiency that would preclude the use of the recombinant urate oxidase enzyme rasburicase. Patients should be evaluated for coinfections, including human immunodeficiency virus, hepatitis B virus, and hepatitis C virus. Additionally, all patients with aggressive ATLL that are potentially curable candidates for allogeneic stem cell transplant should have a human leukocyte antigen (HLA) typing of their siblings immediately after diagnosis [43], since this process can take time and remissions after chemotherapy are often transient.

All aggressive ATLL patients should have imaging to evaluate the extent of lymphadenopathy (LAD), splenomegaly, organ infiltration, and skeletal involvement. Ann Arbor clinical staging is used in both acute and lymphomatous ATLL subtypes. When circulating ATLL cells are visualized in peripheral blood, the patient has stage IV disease but still requires imaging at baseline. Imaging with either computed tomography (CT) with intravenous contrast or positron-emission tomography-computed tomography (PET-CT) is adequate; however, given the rapid progression of this disease, treatment should not be delayed to obtain PET imaging unless it is readily available. Aggressive ATLL often invades the CNS; therefore, all newly diagnosed patients with either the acute or lymphomatous ATLL subtypes should have brain imaging (CT or MRI), along with a lumbar puncture (LP) sent for

cytology and flow cytometry [42]. Intrathecal chemotherapy should be given at the time of the initial LP [44].

Lastly, the histopathological patterns of ATLL vary and mimic different types of T-cell lymphoma. The differential diagnosis of ATLL includes mature T-cell neoplasms such as peripheral T-cell lymphoma not otherwise specified (PTCL-NOS), anaplastic large cell lymphoma (ALCL), angioimmunoblastic T-cell lymphoma (AITL), and even Hodgkin lymphoma (HL). Because of frequent dermatologic manifestations and a leukemic component, ATLL can also be confused with cutaneous T-cell lymphomas (CTCL). Importantly, though, in the World Health Organization's classification, the pathologists can only diagnose this disease if they are aware of the HTLV-1 status [45, 46].

Prognosis

ATLL carries a dismal prognosis and is essentially incurable by conventional drugs. Since its initial description in the 1970s until Shimoyama published his review in 1991, patients with acute and lymphomatous ATLL subtypes had a median survival (MS) time of just 6 and 10 months, respectively [32]. The largest updated retrospective Japanese study published by Katsuya et al. [47] included 1594 patients treated with modern aggressive therapies and reported MS times of 8.3 and 10.6 months for acute and lymphomatous types, respectively. The MS times for the chronic and smoldering types were 31.5 months and 55 months, respectively. The 4-year overall survival (OS) rates for acute, lymphomatous, chronic, and smoldering subtypes were 11%, 16%, 36%, and 52%, respectively [47]. Although there is some improvement in the 4-year OS when comparing both studies (except for smoldering subtype that had a lower than expected OS), the long-term prognosis of ATLL remains poor, thus urging the development of novel therapeutic strategies for this disease.

Factors that have been associated with a poor prognosis in aggressive ATLL include high expression of the Ki67 antigen [40], high serum levels of calcium, parathyroid hormone-related protein, lactate dehydrogenase, thymidine kinase, soluble interleukin-2 receptor (sIL-2R), β2-microglobulin, and neuron-specific enolase. These have been particularly associated with the acute ATLL subtype [48–51]. Based on these data, researchers have developed prognostic scores. The most recent study by Katsuya et al. included 807 patients with newly diagnosed aggressive ATLL (acute and lymphomatous subtypes) [52]. The Ann Arbor stage (stage III/IV, 2 points), performance status (ECOG score 2–4, 1 point), and three continuous variables (age greater than 70, serum albumin level less than 3.5 g/dL, and sIL-2R level greater than 20,000 U/mL; each 1 point) were identified as independent poor prognostic factors. A low score (0–2 points) correlated with a median OS of 16.2 months, an intermediate score (3–4 points) correlated with a median OS of 7 months, and a high score (5–6 points) correlated with a median OS of 4.6 months [52].

Additionally, several studies have identified other poor prognostic factors in aggressive ATLL such as bone marrow involvement, skin involvement, and monocytosis [53]. Eosinophilia [54], high levels of serum LDH and serum urea, and low

levels of serum albumin were associated with poor prognosis in chronic ATLL subtype (also known as "chronic ATLL with unfavorable features") [48]. CD30 positivity has been associated with poor prognosis in the acute and chronic with unfavorable feature subtypes (MS time in the CD30+ and CD30− groups were 10.1 weeks vs. 33.7 weeks, respectively) [55], but not in the lymphomatous ATLL subtype. Expression of c-Rel and interferon regulatory factor-4 (IRF-4 also known as MUM-1 or multiple myeloma oncogene-1) has also been associated with antiviral resistance and poor prognosis [55]. Lastly, CC chemokine receptor 4 (CCR4) expression has been associated with skin involvement and shorter overall survival (OS; median 9.5 months) compared with CCR4-negative (20.6 months) patients [56].

Conventional Treatment Approach

Antiretroviral Therapy

The treatment of ATLL remains challenging and is based on the clinical subtype. In several countries, including Japan, patients with aggressive ATLL (acute, lymphomatous, and chronic with unfavorable feature subtypes) often receive chemotherapy as first-line treatment; in contrast, in the United States, Europe, and some South American countries (e.g., Brazil and Peru), zidovudine (AZT) and interferon-α (IFN) are considered the first-line treatment for non-lymphomatous subtypes, and it is recommended under the National Comprehensive Cancer Network treatment guidelines [48, 57]. Patients with smoldering and favorable chronic subtypes are either observed or started on AZT-IFN [51]. In these groups, narrowband ultraviolet B (NB-UVB) phototherapy can be used to treat symptomatic, superficial skin lesions, and PUVA (psoralen and ultraviolet A) can treat symptomatic, infiltrated skin lesions [58, 59]. One study showed improved survival in those with smoldering ATLL treated with phototherapy combined with oral etoposide (25–75 mg/day for 2–4 weeks with a 1-week interval or on alternate weeks) [60]. Notably, treating smoldering and favorable chronic ATLL with frontline chemotherapy has shown worse survival [51].

The use of AZT-IFN was proposed in 1995 by Gill PS et al. as an attempt to improve mortality in ATLL patients given the short survival despite the use of cytotoxic chemotherapy [61]. The study showed a good response even in patients in whom prior cytotoxic chemotherapy failed. Subsequent studies have supported this finding. The only prospective study to evaluate the efficacy of AZT-IFN in ATLL was a small phase II trial that included 13 frontline patients and 6 relapsed patients [67]. The study only included the aggressive ATLL subtypes (15 acute and 4 lymphomatous). For the 17 patients with evaluable tumor, 13 responses were obtained with 9 complete remissions (CR) and 4 partial remissions (PR). The overall response rate (ORR) was 92% for patients who received AZT-IFN as first-line therapy (58% CR and 33% PR). The median event-free survival (EFS) was 7 months (10 months with AZT-IFN as first-line and 2 months when used after chemotherapy). Median overall survival (OS) was 11 months, with a 28-month survival for patients who

entered CR [62]. Despite impressive responses, most of the patients ultimately relapsed and required further treatment. A meta-analysis by Bazarbachi et al. evaluated the effect of AZT-IFN in 254 patients from four Western countries [63]. Patients with chronic and smoldering ATLL that were initially treated with AZT-IFN had a 5-year OS of 100% and those with acute ATLL who achieved a complete response (CR) while on AZT-IFN had a 5-year survival of 82%. In June 2013, the "16th International Conference on HTLV-1" held in Montreal summarized these findings and concluded that AZT-IFN was effective in the leukemic forms of ATLL and should be considered the first-line therapy in this setting; chemotherapy was only recommended if there was no response to AZT-IFN [64]. Another study has evaluated the role of concurrent chemotherapy and AZT-IFN, which has shown some advantage in aggressive ATLL [65]. Arsenic trioxide may induce cell-cycle arrest and apoptosis in leukemic ATLL cells and has been studied in combination with IFN [66] and with AZT-IFN [67]. The latter study showed an overall response rate (ORR) of 100% in chronic ATLL [67]. Although promising, more prospective data are required to better assess these results.

Chemotherapy

Several combinations of chemotherapeutic agents have been evaluated among ATLL patients. The most commonly used chemotherapy regimens are CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), CHOEP (cyclophosphamide, doxorubicin, etoposide, vincristine and prednisone), VCAP-AMP-VECP (vincristine, cyclophosphamide, doxorubicin, prednisone-doxorubicin, ranimustine, and prednisone-vindesine, etoposide, carboplatin, prednisone), ATL-G-CSF (vincristine, vindesine, doxorubicin, mitoxantrone, cyclophosphamide, etoposide, ranimustine, and prednisolone with prophylactic support by granulocyte colony-stimulating factor), and modified EPOCH (etoposide, prednisolone, vincristine, carboplatin, and doxorubicin; carboplatin is substituted for cyclophosphamide). Despite intensive therapy, MS only ranges between 6 and 8.5 months [40, 42, 47, 48, 68, 69]. The Japanese Clinical Oncology Group (JCOG) has conducted several clinical trials assessing different chemotherapy regimens. A representative study from this group was published by Tsukasaki K et al. in 2007 and showed good results with the VCAP-AMP-VECP regimen (also known as LSG-15), when compared to biweekly CHOP for aggressive ATLL subtypes; a complete response rate of 40% vs. 25% and a MS of 13 vs. 11 months were observed [64]. This regimen is currently the standard of care for aggressive ATLL in Japan, although with significant toxicity (including three treatment-related deaths). As some of these drugs are not available in the United States, regimens like dose-adjusted EPOCH, CHOP, CHOEP, and hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone-methotrexate, cytarabine) are acceptable alternatives [57, 70]. Because of frequent CNS involvement in aggressive ATLL subtypes (ranging from 10% to 25%), intrathecal chemotherapy prophylaxis is recommended [44, 57].

Novel Agents

Conventional approaches for the treatment of ATLL have failed to achieve long-term survival. Because of this, there has been a shift to evaluate agents with a novel mechanism of action. Several of these agents have been studied for the treatment of ATLL, but none are currently approved by the Food and Drug Administration (FDA). For the remainder of this chapter, we will focus on the research behind these novel agents. Table 9.1 compares various treatments for frontline and relapsed ATLL. Table 9.2 lists ongoing clinical trials in the United States with various novel agents.

Monoclonal Antibody Therapy

Brentuximab Vedotin

Brentuximab vedotin (BV) is an antibody-drug conjugate that combines an anti-CD30 monoclonal antibody with the microtubule disrupting agent, monomethyl auristatin E (MMAE) [71]. BV is an effective treatment option for Hodgkin lymphoma (HL), anaplastic large cell lymphoma (ALCL), CD30+ peripheral T-cell lymphoma (PTCL), CD30+ cutaneous T-cell lymphoma (CTCL), and CD30+ diffuse large B-cell lymphoma (DLBCL) [71–76]. However, the impact of BV in ATLL has not been established. As previously discussed, a study published by Campuzano-Zuluaga et al. in 2013 showed a variable CD30 expression in ATLL specimens [55] with 22.1% of ATLL cases positive for CD30. Importantly, the cutoff for CD30 expression in this study was high at 30%. BV has been shown to be effective in cases

Table 9.1 Treatment regimens used in frontline and relapsed setting

Treatment regimen	*N*	Study	ORR (%)	CR (%)	PFS	OS
AZT-IFN	19	Phase II	76.5	53	10 months	11 months
CHOP-14	61	Randomized phase II	66	21	5.4	11
LSG15	57	Randomized phase II	72	40	7	13
Lenalidomide	26	Phase II	42	19	3.8	20.3
BV-CHP	2	Phase I	100	100	18.5	NR
Mogamulizumab	27	Phase II	50	31	5.2	13.7
Mogamulizumab-LSG15	29	Randomized phase II	86	52	8.5	NR

AZT-IFN zidovudine-interferon-alpha; *BV-CHEP* brentuximab vedotin with cyclophosphamide, doxorubicin, etoposide, prednisone; *CHOP-14* cyclophosphamide, doxorubicin, vincristine, and prednisone as a 14-day cycle; *CR* complete response; *LSG-15* VCAP-AMP-VECP (vincristine, cyclophosphamide, doxorubicin, prednisone-doxorubicin, ranimustine, and prednisone-vindesine, etoposide, carboplatin, prednisone); *N* number of patients, *ORR* overall response rate; *OS* overall survival, *PFS* progression-free survival

Table 9.2 Ongoing clinical trials available for ATLL patients in the United States

Status	Study title	Conditions	Interventions	Location
Recruiting	BV-CHEP chemotherapy for frontline treatment of adult T-cell leukemia or lymphoma	ATLL	Drug: BV-CHEP	Chapel Hill, North Carolina (UNC Hospital and Clinics) and other centers in Boston and NYC
Recruiting	Belinostat therapy with zidovudine for frontline treatment of adult T-cell leukemia-lymphoma	ATLL	Drugs: belinostat, AZT-IFN, pegylated-IFN	Miami, FL (University of Miami)
Recruiting	Subcutaneous recombinant human IL-15 (s.c. rhIL-15) and alemtuzumab for people with refractory or relapsed chronic and acute adult T-cell leukemia (ATL)	ATLL	Biological: IL-15 plus alemtuzumab	Bethesda, Maryland (NIH)
Recruiting	Ruxolitinib for adult T-cell leukemia	ATLL	Drug: ruxolitinib	Bethesda, Maryland (NIH)

ATLL adult T-cell leukemia/lymphoma, *AZT* zidovudine, *BV-CHEP* brentuximab vedotin with cyclophosphamide, doxorubicin, etoposide, prednisone, *IFN* interferon-alpha, *IL-15* interleukin 15, *NIH* National Institutes of Health

of CTCL with levels of CD30 expression lower than 10% [75]. In 2014, Fanale et al., as part of a Phase I multicenter clinical trial that evaluated the safety and efficacy of BV in CD30-positive PTCL [77], two patients with ATLL were treated with BV-CHP (cyclophosphamide, doxorubicin, and prednisone) and achieved a complete response (one patient was stage IV with an International Prognostic Index [IPI] score of 3% and 25% of CD30 expression with a progression-free survival [PFS] of 7.1 months, and one patient was stage IV with an IPI score of 5% and 98% CD30 expression with a PFS of 22.8 months) [77]. Updated results from this study were recently published, and one ATLL patient remained in remission with a PFS of 56.7+ months and an OS of 64.1+ months [78]. At present, a Phase III trial (ECHELON-2 trial) comparing BV-CHP with CHOP in the initial treatment of CD30-positive mature T-cell lymphomas is not recruiting patients as of July 2017, but data analysis is ongoing [79, 80]. Two promising Phase II clinical trials are currently recruiting patients. One trial, based on the west coast, is assessing BV and combination chemotherapy in the treatment of patients with CD30-positive PTCL that will include ATLL patients [81]. The other trial will target the ATLL population specifically and is focused where the majority of ATLL patients are located in the United States, on the Eastern Seaboard [84]. This trial is based at the University of North Carolina at Chapel Hill and will collaborate with Rare Lymphoma Working Group (RLWG) sites in Boston to capture more cases of ATLL. This study will evaluate four to six cycles of the regimen BV-CHEP (brentuximab vedotin, cyclophosphamide, doxorubicin, etoposide, and prednisone) in ATLL patients. Patients

who are eligible for allogeneic transplant will be consolidated with this modality in the first complete response (CR1). Patients who are not eligible for transplant but are CD30-positive will continue maintenance BV after they complete six cycles of BV-CHEP. CD30-negative patients who are not transplant eligible will complete six cycles of BV-CHEP and then enter a follow-up period.

Mogamulizumab

Mogamulizumab is a humanized monoclonal antibody targeting CC chemokine receptor 4 (CCR4), which was found to be overexpressed in 99 (88.3%) out of 103 patients with ATLL and was associated with a poor prognosis [82]. Mogamulizumab was approved in Japan in 2012 based on a Phase II trial for the treatment of relapsed or refractory ATLL [83, 84]. The study included 27 CCR4-positive patients with aggressive, relapsed ATLL, and mogamulizumab was given at a dose of 1.0 mg/kg intravenous weekly for 8 weeks. The median PFS was 5.2 months and a median OS of 13.7 months. Common adverse events were cytopenias, fever, rash, chills, and one case of erythema multiforme. In 2015, Ishida et al. conducted a Phase II randomized trial comparing mogamulizumab in combination with LSG-15 regimen versus LSG-15 alone in newly diagnosed patients with aggressive ATLL [85]. The study showed a complete response (CR) rate of 52% vs. 33% and a median PFS of 8.5 months vs. 6.3 months, in the combination arm vs. the LSG15-alone arm, respectively. Median OS was not reached in either arm after 413 and 502 days of follow-up, respectively [85]. In October 2016, a retrospective study evaluated 82 ATLL patients who underwent allogeneic stem cell transplant who received mogamulizumab-based regimen as first-line therapy, found a significant association between mogamulizumab, and increased risk of grade 3–4 acute graft-versus-host disease (GVHD; relative risk, 1.80; $p < 0.01$), nonrelapse mortality ($p < 0.01$), and decreased overall survival ($p < 0.01$) [89]. Based on these findings, mogamulizumab should be used cautiously in transplant-eligible patients. In October 2017, an updated follow-up analysis of the Phase I and Phase II mogamulizumab studies was published [86]. The analysis reported a 3-year OS of 31% and 23%, in the Phase I and Phase II studies, respectively. An interesting conclusion from this study was that patients who developed a grade 2 or greater skin rash as an immune-related adverse event had a better PFS and OS (1-year PFS of 0% vs. 50% and 3-year OS of 8% vs. 36%, in patients with grade 1 vs. ≥ grade 2 skin rash, respectively) [86].

Alemtuzumab

Alemtuzumab is a monoclonal antibody that binds to CD52, an antigen present on normal and pathologic B- and T-cells. It has shown activity in chronic lymphocytic leukemia (CLL), cutaneous T-cell lymphoma (CTCL), and PTCL [87]. ATLL cells frequently express CD52 as compared to other PTCLs [88]. The combination of alemtuzumab with a standard-dose CHOP regimen as a first-line treatment was

studied in 24 patients with PTCL and showed a CR rate in 17 (71%) patients, with an overall median duration of response of 11 months; however, it was associated with CMV reactivation [89]. In the United States, a phase II study conducted by the National Institute of Health treated 29 patients with chronic, acute, or lymphomatous-type ATLL with alemtuzumab as frontline therapy [90]. Alemtuzumab induced responses in patients with acute HTLV-1-associated ATLL (15 of 29 patients); however, duration of responses, progression-free survival, and overall survival were short (median response duration 1.4 months, PFS 2.0 months, OS 5.9 months). Although alemtuzumab has shown activity in ATLL, the modest survival rates and risk of CMV infection limit its effectiveness in treating ATLL.

Daclizumab

Because CD25 (interleukin-2 receptor alpha chain) is universally expressed in ATLL, it is an obvious target for monoclonal antibody therapy. An anti-CD25 agent, daclizumab, which is used to prevent rejection in organ transplantation, was evaluated in two different ATLL clinical trials. One study evaluated daclizumab alone (8 mg/kg) in 34 patients and found no response in the 18 patients with aggressive ATLL [91], and the second study, a Phase II trial, evaluated 15 patients with ATLL treated with a lower dose of daclizumab (1 mg/kg) in combination with standard CHOP chemotherapy and showed median OS of 10 months, with CR and PR of 33% and 20%, respectively [92]. Taken together, the response to daclizumab was not as robust as was hoped; therefore use of this agent has not been widely adopted.

Immunomodulatory Therapy

Lenalidomide is an immunomodulatory agent currently used in multiple hematologic malignancies. Its role in ATLL has been evaluated in Phase I and Phase II trials in the relapsed/recurrent ATLL setting, demonstrating clinically meaningful antitumor activity [93–95]. An updated follow-up analysis from the Phase II trial (ATLL-002) by Ishida et al. was published in December 2016 [95]. Twenty-six ATLL patients (median age 68.5 years) with aggressive ATLL ($n = 22$) and chronic unfavorable ($n = 4$) subtypes, which had relapsed after at least one prior therapy, were included in this study and received lenalidomide 25 mg oral daily continuously until disease progression or unacceptable toxicity. The median PFS and OS were 3.8 and 20.3 months, respectively. The CR and OR rates were 15% and 42%, respectively. Responses according to disease subtype were 33% (5 of 15) for acute, 57% (4 of 7) for lymphoma, and 50% (2 of 4) for unfavorable chronic ATLL. Responses according to disease site were 31% for target (nodal and extranodal) lesions, 75% for skin, and 60% for peripheral blood. Responses were also analyzed according to prior mogamulizumab treatment and were 18% in patients who had previously received mogamulizumab and 60% in mogamulizumab-naïve patients [95]. Based on these results, further investigations of lenalidomide in ATLL are warranted.

PD-1/PD-L1 Pathway

Programmed cell death protein 1 (PD-1) and programmed cell death ligand 1 (PD-L1) are expressed on both tumor and tumor-infiltrating nonmalignant cells in lymphoid malignancies [96, 97]. Increasing data have shown that PD-1 is expressed at a higher level in T-cells from tumor patients [98]. The presence of high levels of plasma-soluble PD-L1 and PD-L1 expression on lymphoma cells is associated with poor overall survival (OS) and is considered an important biomarker in diffuse large B-cell lymphoma (DLBCL) [99, 100]; additionally, blockade therapy of the PD-1/PD-L1 pathway showed a remarkable effect for Hodgkin lymphoma (HL) [101]. These results suggest that the PD-1/PD-L1 pathway might support tumor cell survival and that blockade of this pathway could be an effective therapeutic method in lymphoid malignancies other than DLBCL and HL. Studies performed on ATLL cells have shown increased PD-1 expression on both CD4+CD25+ and CD4+CD25− T-cells, but not in CD8+T cells [102, 103]. Similarly, higher expression of PD-L1 has been found in the majority of different hematological malignant cells, including ATLL cells [103, 104]. A study published in September 2016 by Miyoshi et al. performed PD-L1 immunostaining in 135 ATLL biopsy samples (51%, 48%, and 1% were acute, lymphomatous, and smoldering subtypes, respectively) [104]. They observed that PD-L1 (+) ATLL had inferior OS compared with PD-L1 (−) ATLL (MS times 7.5 vs. 14.5 months, respectively; $p = 0.0085$). This is the first report describing the clinicopathological features and outcomes of PD-L1 expression in ATLL. In the United States, the National Cancer Institute (NCI) conducted a phase II clinical trial to evaluate nivolumab in the treatment of ATLL patients who had an increased mutational load and overexpression of PD-L1 [105]. After treating the first three patients, they developed worsening leukocytosis, hypercalcemia, renal insufficiency, and increased LDH levels after a single dose of nivolumab [106]. The study was closed due to evidence of rapid disease progression. More studies are needed to elucidate the role of PD-L1 in ATLL.

HDAC Inhibitors

Histone deacetylases (HDACs) are enzymes involved in the remodeling of chromatin and play a key role in the epigenetic regulation of gene expression. Histone deacetylase (HDAC) inhibitors induce the hyperacetylation of nonhistone proteins as well as nucleosomal histones resulting in the expression of repressed genes involved in growth arrest, terminal differentiation, and/or apoptosis among cancer cells. HDAC inhibitors such as vorinostat, romidepsin (depsipeptide), and panobinostat (LBH589) have shown activity in preclinical and clinical studies against T-cell malignancies including ATLL [107, 108]. LBH589 had a significant anti-ATL effect in vitro and in mice. However, a phase II study for CTCL and indolent ATLL in Japan was terminated because of severe infections associated with the shrinkage of skin tumors and formation of ulcers in patients with ATLL [108].

IL-2 Receptor

Denileukin diftitox, an interleukin-2-diphtheria toxin fusion protein targeting IL-2 receptor-expressing malignant T lymphocytes, has also shown efficacy as a single agent [109] or in combination with CHOP with promising results for PTCL [110]. Some ATLL cases successfully treated with this agent have been reported [111].

Anti-Tax Vaccine

Cytotoxic T lymphocyte (CTL) against HTLV-1 Tax has been demonstrated to play a vital role in controlling HTLV-1-infected cells in HTLV-1-carrier patients [112]. Since there is a long latency period between HTLV-1 infection and the onset of ATLL, mechanisms for leukemogenesis in the infected cells present in a multistep fashion; hence, immunization may play a role against it. In Japan, Suehiro et al. developed an anti-ATLL therapeutic vaccine consisting of autologous dendritic cells that is pulsed with Tax peptides (Tax-DC) [112]. The vaccination protocol was completed with three injections at a 2-week interval. This approach was studied in a pilot study of three previously treated ATLL patients (unknown subtypes). All patients had a Tax-specific CTL response, and two patients had a partial response at 8 weeks, which was maintained for at least 19 months. The third patient had stable disease at 8 weeks and then slowly progressed [112]. From this study, investigators have conducted a clinical trial of Tax-DC vaccine combined with anti-CCR4 antibody to enhance the efficacy of the vaccine as next-generation immunotherapy [113]. Results have not been presented yet.

Allogeneic Stem Cell Transplantation

Considering the unsatisfactory results of standard treatments, the role of stem cell transplantation (SCT) in aggressive ATLL has been investigated. Initially, autologous stem cell transplantation (auto-SCT) was attempted, but it did not yield success [114]. In 1996 Borg et al. reported the first successful allogeneic stem cell transplant (allo-SCT) for the treatment of ATLL. This patient remained in a CR with no evidence of disease at 23 months post-transplant [115]. Since that first case, several reports have been published by various Japanese groups mainly in form of retrospective series and Phase I clinical trials. Although the earlier studies were notable for a high incidence of serious infections and other complications, recent experience has been more encouraging. In 2013, The Japan Society for Hematopoietic Cell Transplantation reported that by 2012, more than 1000 ATLL patients had received allo-SCT [116] with an estimate of approximately 120 ATLL patients transplanted a year. This study showed that patients receiving an allogeneic transplant with an HLA-matched donor had a 3-year OS rate of 41% [122]. In another study, researchers found that acute grade I/II GVHD was significantly associated

with a longer OS, which was likely from a graft-versus-leukemia effect [117]. Lastly, a study showed no significant difference between myeloablative conditioning (MAC) and reduced-intensity conditioning (RIC) in OS, although there was a mild trend for superior OS with RIC in older patients [118].

Regarding non-Japanese experience, in October 2014, Bazarbachi et al. reported 21 ATLL patients (7 acute, 12 lymphomatous subtypes) that underwent SCT (4 auto-SCT and 17 allo-SCT) [119]. All patients that underwent auto-SCT rapidly died from ATLL. Of 17 patients who underwent allo-SCT (4 myeloablative, 13 reduced intensity), 6 are still alive at the time of this publication (4 were in CR at SCT), and 11 patients died within 2 years (8 from relapse/progression and 3 from transplant toxicity) [119]. The study concluded that, overall, these results indicate that allo-SCT but not auto-SCT may salvage a subset of ATLL patients with relapsed disease, supporting the existence of graft-versus-leukemia/ATLL effect in non-Japanese patients.

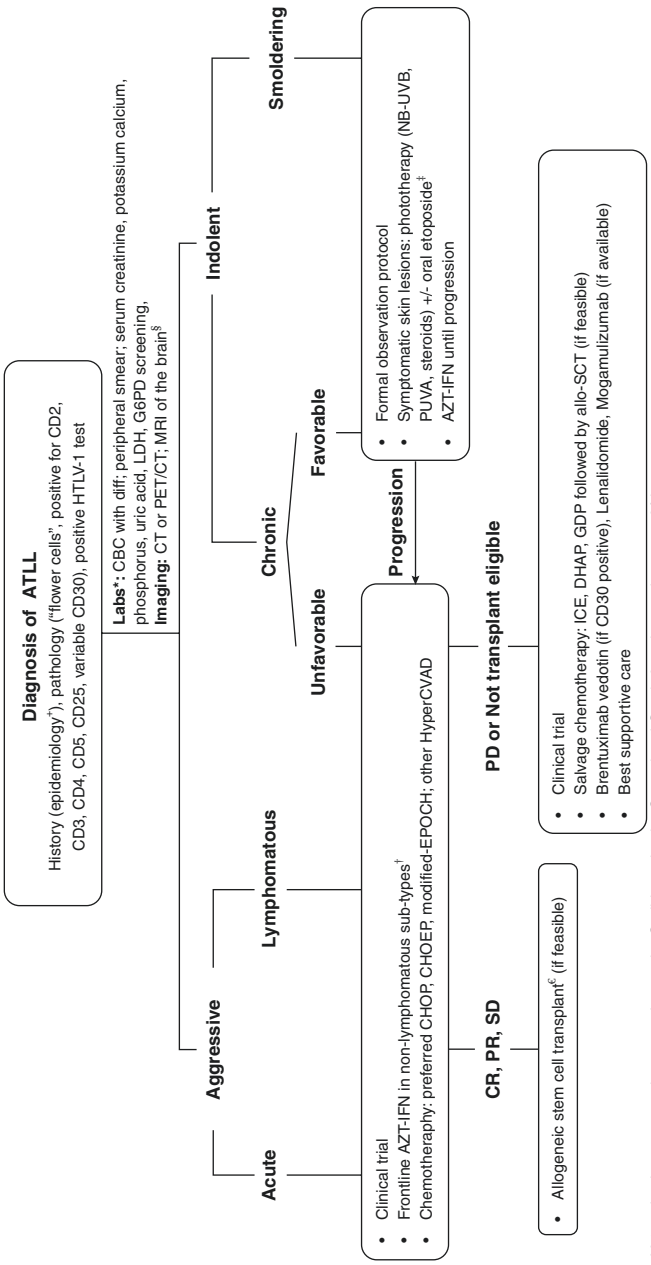
Lastly, the largest updated retrospective study published in 2015 by Katsuya et al. reported 214 patients (of age 65 years or younger) with acute and lymphoma subtypes that underwent allo-SCT after first remission ($n = 117$), in primary refractory ATLL ($n = 56$), and in the relapsed setting ($n = 41$) [5]. The MS time after transplant and 4-year OS were 5.9 months and 26%, respectively. The MS times from transplantation showed differences when analyzed by clinical status before transplant. Patients survived 22 months when transplanted in first remission vs. 3 months when the transplant occurred in primary refractory or relapsed disease. Regarding ongoing clinical trials, there is one clinical trial recruiting only ATLL patients at the University Hospital Center of Martinique in the Caribbean; the study will evaluate high-risk adult T-cell leukemia/lymphoma (ATLL-HR) treated with AZT-IFN, AZT-IFN and CHOP, and AZT-DHAP (dexamethasone, cytarabine, and cisplatin) followed by allo-SCT (ATLL-HR-01) [120].

Recommended Treatment Approach in Frontline and Refractory/Relapsed Disease

Treating ATLL represents a challenge because there are few data based on randomized controlled trials due to its rarity. Additionally, several of the abovementioned drugs (e.g., ranimustine, vindesine) are not available in the United States. Figure 9.3 summarizes a treatment strategy in frontline and in refractory/relapsed setting based on available data and the National Comprehensive Cancer Network (NCCN) recommendations.

Frontline

At present, treatment options for ATLL are suboptimal, and all patients diagnosed with ATLL should be evaluated for clinical trials. Regarding current treatment recommendations for ATLL, as previously discussed, it will depend on the clinical



+ HTL V-1 endemic areas: southwestern Japan, the Caribbean basin, Central and South America, and western Africa

* Eosinophilia and monocytosis related to worse prognosis. Watch for hypercalcemia, and TLS syntrome (screen for G6PD deficiency to prevent hemolsis with rasburicase)

§ Obtain in aggressive ATLL (acute and lymphomatous) along with LP with prophylactic IT chemotherapy given increased risk for CNS involvement

‡ In smoldering sub-type, oral etoposide 25 to 75 mg/day for 2 to 4 weeks with a one-week interval or on alternate weeks (Reference 60)

† Treatment with AZT-IFN should be continued only if response, If not response after few weeks (most studies 1-2 weeks), consider switching to multiagent chemotherapy

€ Consider myeloablative conditioning if younger than 50 years, and reduced-intensity conditioning if older than 50 years (Reference 118)

Allo-SCT: Allogenetic stem cell transplantation; **AZT-IFN:** Zidovudine-Interferon alpha; **CBC with diff:** Complete blood count with differential; **CHOP:** Cyclophosphamide, doxorubicin, vincristine, and prednisone; **CHOEP:** Cyclophosphamide, doxorubicin, etoposide, vincristine and prednisone); **CR:** Complete response; **CT:** Completed Tomography; **G6PD:** Glucose-6-Phosphate Dehydrogenase; **DHAP:** dexamethasone, cytarabine, cisplatin; **GDP:** gemcitabine, dexamethasone, cisplatin; **Hyper-CVAD:** Cyclophosphamide, vincristine, doxorubicin, and dexamethasone - methotrexate, cytarabine; **ICE:** Ifosfamide, carboplatin, etoposide; **Modified EPOCH:** Etoposide, prednisolone, vincristine, carboplatin, and doxorubicin; carboplatin is substituted for cyclophosphamide; **NB-UVB:** Narrowband ultraviolet B; **PD:** Progessive disease; **PET/CT:** Positron Emission Tomography/Computed Tomography; **PR:** Partial response; **PUVA:** Psoralen and ultraviolet A; **TLS:** Tumor lysis syndrome; **SD:** Stabledisease

Fig. 9.3 Adapted treatment strategy for ATLL

subtype at diagnosis. Patients with aggressive ATLL should receive immediate treatment with either antiviral therapy with zidovudine and interferon-α (AZT-IFN) (except for those with the lymphomatous subtype) or multiagent chemotherapy [47, 48, 51, 57, 64, 65, 63]. Available chemotherapy regimens recommended by the NCCN are CHOP, CHOEP, modified EPOCH, and hyper-CVAD. Including etoposide in the regimen is reasonable for patients under the age of 60, based on an extrapolation from studies in PTCL [121]. Because of frequent CNS involvement and CNS relapse in aggressive ATLL subtypes, intrathecal chemotherapy prophylaxis is recommended [44, 57]. Any patient achieving a CR (or PR) should be evaluated for an allogeneic stem cell transplantation (allo-SCT), which is particularly effective in young patients with good performance status [47, 118, 119, 122]. In indolent ATLL, AZT-IFN can be initiated at diagnosis or on progression of disease. If surveillance is pursued, patients must be followed very closely for progression. If skin lesions are present, skin-directed therapy with topical steroids, and narrowband ultraviolet B (NB-UVB) phototherapy for superficial lesions, and PUVA (psoralen and ultraviolet A) for more infiltrated lesions are recommended [58, 59].

Refractory/Relapsed Disease

ATLL patients with relapsed or refractory disease should be evaluated for clinical trials. In the aggressive ATLL subtypes, if a patient fails to respond to frontline chemotherapy prior to allo-SCT, the patient should be switched to a salvage regimen (ICE, DHAP, GDP), and if remission/response is achieved, then the patient should be evaluated for allo-SCT. If the patient relapsed after allo-SCT or the patient is not eligible for transplant, CD30 positivity should be evaluated. If positive, patients should receive a trial of brentuximab vedotin. Lenalidomide is another reasonable option in the relapsed setting. Mogamulizumab is an option that should be used in regions where it is available. Other relapsed regimens used in PTCL can also be extrapolated to ATLL, but these will likely have limited effect.

Supportive Care

ATLL is unique in that there are many severe complications that are associated with the disease. Common complications in ATLL include hypercalcemia, tumor lysis syndrome, and severe infections. The hypercalcemia associated with ATLL is often severe, with calcium levels over 20 mg/dL. Treatment should include aggressive hydration and the early administration of a bisphosphonate. Opportunistic infections caused by immunosuppression are common in ATLL. Prophylaxis for *pneumocystis* pneumonia, herpes simplex/zoster virus,

fungal infections, and gram negative bacterial infections should be strongly considered for all patients. Patients should be screened for *Strongyloides stercoralis* infection and should receive treatment for any positive screening given the risk for hyperinfection syndrome by *Strongyloides stercoralis* [123–126]. Tuberculosis screening should be considered for patients who are high risk for prior exposure. Tumor lysis syndrome is a known complication in all aggressive hematologic malignancies and can be fatal; hence, early and aggressive intravenous hydration, along with allopurinol administration, and G6PD deficiency screening are recommended. If the patient does not have G6PD deficiency, rasburicase should be considered for severe TLS.

Conclusion

Adult T-cell leukemia/lymphoma (ATLL) is a rare T-cell neoplasm caused by the human T-cell lymphotropic virus type 1 (HTLV-1). ATLL continues to have a poor outcome with currently available therapies. ATLL can be divided into the aggressive (acute, lymphomatous, and chronic with unfavorable features) and indolent (smoldering and chronic with favorable features) subtypes, which influence treatment strategies. AZT-IFN is a reasonable first-line option in patients with the smoldering, chronic, or non-bulky acute subtypes. Chemotherapy remains the preferred choice for lymphomatous or bulky acute ATLL. The current therapeutic approach in the United States is to give a CHOP-like regimen containing etoposide (either CHOEP or dose-adjusted EPOCH), with the intent to achieve remission and proceed to allogeneic transplant. Novel therapeutic approaches include the use of antibody-drug conjugates (brentuximab vedotin), anti-CCR4 therapy, immunomodulatory therapy, and anti-TAX vaccines. The Rare Lymphoma Working Group is focusing future research on multi-institutional clinical trial participation because of the rarity of this disease. We are hopeful that a collaborative effort can help find an effective therapeutic approach to improve survival in ATLL.

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