

Novel treatments of adult t cell leukemia lymphoma

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Introduction

Adult T Cell Leukemia: Epidemiology, Pathophysiology, Clinical Presentation and Classification

Adult T cell leukemia (ATL) was discovered in Japan in 1976 ([Takatsuki et al., 1976](#)), and was associated with the Human T cell leukemia virus type I (HTLV-I) in 1980 ([Poiesz et al., 1981](#)). ATL is an aggressive malignancy characterized by the clonal expansion of mature activated T cells generally CD3⁺ CD4⁺ CD5⁺ CD7⁻ CD8⁻ CD25⁺ ([Uchiyama et al., 1983](#) ; [Waldmann et al., 1984](#) ; [Dasanu, 2011](#) ; [Tian et al., 2011](#)). It occurs in 1-5% of the infected individuals, after a very long latency period which may exceed 50 years ([Gessain and Mahieux, 2000](#) ; [Gessain, 2011](#) ; [Ishitsuka and Tamura, 2014](#) ; [Watanabe, 2017](#) ; [Bangham, 2018](#)). HTLV-I is the first oncogenic retrovirus allied with a human disease. It infects around 10-20 million people worldwide, and is endemic in several countries including Southern Japan, the Caribbean islands, Central and Latin America, Romania, the Middle East (chiefly Iran), Intertropical Africa, MelanAsia, and Central Australia ([Gessain and Mahieux, 2000](#) ; [Laperche et al., 2009](#) ; [Gessain, 2011](#) ; [Bangham, 2018](#) ; [Afonso et al., 2019](#)). Alarmingly, a rising incidence of ATL was reported in non-endemic regions including the United States and the North of Japan ([Chihara et al., 2012](#) ; [Malpica et al., 2018](#)).

The oligoclonal expansion of HTLV-I infected cells results from the expression of the viral transactivator Tax ([Wattel et al., 1995](#) ; [Mortreux et al., 2001](#)).

Tax oncoprotein plays a critical role in ATL initiation and leukemogenesis through alteration of many cellular pathways, following activation of the viral promoter, and creation of an autocrine loop involving interleukin-2 (IL-2), IL-

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15 and their respective receptors ([Bamford et al., 1994](#) ; [Wattel et al., 1995](#) ; [Azimi et al., 1999](#) ; [Mortreux et al., 2001](#)). Tax activates CREB/ATF, AP-1, and NF- κ B transcription factors, upregulates anti-apoptotic proteins, represses p53, DNA polymerase beta, PCNA, and MAD-1 checkpoints and interferes with several cell cycle regulators and DNA repair systems ([Mulloy et al., 1998](#) ; [Kfoury et al., 2005](#) ; [Matsuoka and Jeang, 2011](#)). Indeed, Tax binds to IKK- γ , the regulatory subunit of the IkappaB kinase (IKK) complex ([Yamaoka et al., 1998](#) ; [Harhaj and Sun, 1999](#) ; [Kfoury et al., 2008](#) ; [Wang et al., 2016](#)), resulting in the activation of the NF- κ B pathways and its downstream effector genes (Reviewed in [Kfoury et al., 2005](#)). This induced NF- κ B activation highly depends on Tax post-translational modifications namely ubiquitylation, sumoylation, and urmylation ([Nasr et al., 2006](#) ; [Kfoury et al., 2008](#) , [2011](#) ; [Hleihel et al., 2018](#) , Reviewed in [Kfoury et al., 2012](#)). Furthermore, Tax modulates the microenvironment and increases invasion and extravasation of ATL cells ([El-Sabban et al., 2002](#) ; [Bazarbachi et al., 2004a](#)). Tax down-regulates the expression of various micro RNAs (mi-RNA) including mi-RNA31 known to inhibit the expression of the NF- κ B non-canonical pathway components ([Yamagishi and Watanabe, 2012](#)). Tax transforms T cells *in vitro* , and its expression in T cells of transgenic mice, or in human CD34⁺ stem cells induces leukemia with striking ATL features recapitulating the human disease ([Portis et al., 2001](#) ; [Hasegawa et al., 2006](#) ; [Banerjee et al., 2007](#) ; [Ohsugi et al., 2007](#) ; [Moodad et al., 2018](#)). Tax also induced rough eye phenotype, a hallmark of malignant transformation in Drosophila models ([Shirinian et al., 2015](#)). Although Tax protein expression is very low in most ATL patients, recent *in vitro* data demonstrated that

transient bursts of Tax expression occur sequentially in small fractions of ATL-derived cells ([Billman et al., 2017](#)). Importantly, ATL-derived cells depend on Tax expression for their long-term survival, even when Tax protein is undetectable by western blot ([Dassouki et al., 2015](#) ; [Mahgoub et al., 2018](#)).

Another viral nuclear protein, HBZ, is encoded by the complementary strand of HTLV-I RNA genome ([Larocca et al., 1989](#) ; [Gaudray et al., 2002](#)). HBZ is a negative regulator of Tax-mediated viral transcription ([Gaudray et al., 2002](#)), and its transcript levels positively correlate with HTLV-I proviral load in both ATL patients and asymptomatic carriers ([Saito et al., 2009](#)). Unlike Tax, HBZ is constantly expressed in ATL cells ([Saito et al., 2009](#) ; [Mahieux, 2015](#) ; [Sugata et al., 2015](#)). Although HBZ was shown to promote the proliferation of ATL cells *in vitro* , short hairpin RNA (shRNA) directed against HBZ only results in a modest inhibition of ATL cells proliferation, showing that HBZ is dispensable for the survival of ATL cells ([Satou et al., 2006](#) ; [Arnold et al., 2008](#)). HBZ affects several cellular pathways implicated in cellular proliferation ([Panfil et al., 2016](#)). Unlike Tax, HBZ inhibits NF- κ B, attenuating Tax effect and thus preventing ATL cells senescence ([Panfil et al., 2016](#)). One HBZ transgenic mouse model exhibited transforming features, yet without NF- κ B activation, contrary to human ATL or Tax transgenics ([Yoshida et al., 2008](#) ; [Matsuoka and Green, 2009](#) ; [Saito et al., 2009](#) ; [Matsuoka and Jeang, 2011](#) ; [Zhao and Matsuoka, 2012](#) ; [Ma et al., 2016](#)).

At the clinical level, ATL patients have a heterogeneous presentation from indolent slowly progressive disease to aggressive and life-threatening disease. The Shimoyama classification divides the disease into four major subtypes: smoldering, chronic, lymphoma, and acute ([Shimoyama, 1991](#)). All are characterized by a dismal long-term prognosis and a low median survival rate, ranging between 6 months for the acute subtype and 24 months for the chronic subtype ([Shimoyama, 1991](#)).

Acute ATL accounts for 55–60% of patients ([Shimoyama, 1991](#) ; [Pombo De Oliveira et al., 1999](#) ; [Katsuya et al., 2015](#)). It is characterized by major lymphocytosis of “ flower cells” or “ clover leaf” which are features typical of ATL, lymphadenopathy, hepatosplenomegaly, hypercalcemia, and its related symptoms such as renal dysfunction or neuropsychiatric disturbances ([Tamura et al., 1986](#) ; [Kiyokawa et al., 1987](#)), high lactate dehydrogenase (LDH) ([Yamaguchi et al., 1983](#)) and frequent opportunistic infections due to a profound immunosuppression. These include pneumonia caused by *Pneumocystis carinii* , disseminated cryptosporidiosis and toxoplasmosis, cytomegalovirus, bacterial abscesses and sepsis as well as fungal infection and cytomegalovirus activation ([Ueda et al., 1979](#) ; [Blayney et al., 1983](#) ; [Bunn et al., 1983](#) ; [Verdonck et al., 2007](#)). Skin and visceral lesions in the bone, the gastrointestinal tract and the lung may be also observed.

Lymphoma ATL accounts for around 20–25% of ATL cases ([Shimoyama, 1991](#) ; [Pombo De Oliveira et al., 1999](#) ; [Katsuya et al., 2015](#)). This form is characterized by the same symptoms of the acute subtype, but differs in presenting less than 1% leukemia cells in the peripheral blood, thus the

absence of lymphocytosis. Smoldering ATL subtype accounts for 5–10% of cases ([Shimoyama, 1991](#) ; [Pombo De Oliveira et al., 1999](#) ; [Katsuya et al., 2015](#)) and is characterized by a normal leukocyte count but the presence of 1–5% flower cells. In addition, only skin and lungs may be infiltrated without the involvement of any other viscera. Finally, the chronic ATL subtype accounts for 10–20% of patients ([Shimoyama, 1991](#) ; [Pombo De Oliveira et al., 1999](#) ; [Katsuya et al., 2015](#)), and associates with a high leukocyte count causing lymphadenopathy and hepatosplenomegaly, absence of hypercalcemia, or visceral involvement, normal or slightly increased LDH levels. This subtype is further divided into favorable or unfavorable subgroups. The latter is defined by low serum concentration of albumin, high level of LDH, or high serum urea concentration, as well as high expression of Ki-67 antigen ([Shirono et al., 1989](#) ; [Yamada et al., 2001](#)). It is worth noting that the term “ indolent ATL” refers to smoldering and “ favorable” chronic subtypes, while “ aggressive ATL” includes the acute and lymphoma as well as the “ unfavorable” chronic subtypes.

Classical Therapeutic Options of ATL: Chemotherapy, Antiviral Therapy and Stem Cell Transplantation

Adult T cell leukemia remains a challenging malignancy. The clinical management of ATL and the proposed therapeutic options largely depend on the ATL subtype. The aggressive forms of ATL associate with a dismal prognosis, an intrinsic chemo-resistance, and a profound immunosuppression, associated with secondary opportunistic infections ([Shimoyama, 1991](#) ; [Hermine et al., 1998](#) ; [Bazarbachi et al., 2004b](#) , [2011](#) ; [Tobinai, 2009](#)). Patients with indolent ATL have a better prognosis. In Japan,

these patients were managed with the watch-and-wait policy until progression or with chemotherapy, yet the long term results remain very poor ([Takasaki et al., 2010](#) ; [Hermine et al., 2018](#)).

In addition to the Shimoyama classification, several prognostic factors were identified. For instance, elevated LDH levels, four total involved areas or more, thrombocytopenia, bone marrow involvement, eosinophilia, hypercalcemia, age of 40 or above, p53 mutations, p16 deletions, high IL-15 serum levels, and C-C chemokine receptor 4 (CCR4) expression are nowadays factors that predict poor prognosis ([Tsukasaki et al., 2009](#)). An international consensus report, published in 2009, defined prognosis factors, clinical features, therapeutic strategies, and response criteria for ATL ([Tsukasaki et al., 2009](#)). A recent update was recently published ([Cook et al., 2019](#)).

Standard treatment strategies of ATL include watch and wait policy for indolent ATL, conventional chemotherapy, the combination of two antiviral agents zidovudine (AZT) and interferon-alpha (IFN), and allogeneic hematopoietic stem cell transplantation (HSCT) ([Tsukasaki et al., 2009](#) ; [Bazarbachi et al., 2011](#) ; [Hermine et al., 2018](#) ; [Cook et al., 2019](#)). The different Japanese trials using acute lymphoblastic leukemia or Non Hodgkin lymphoma -inspired chemotherapy regimen clearly demonstrated that ATL cells are chemo-resistant and that chemotherapy had little effect on the survival of ATL patients, specifically those with acute ATL ([Dearden et al., 1991](#) ; [Tanabe et al., 1991](#) ; [Tobinai et al., 1992](#) ; [Tsuda et al., 1994](#) ; [Taguchi et al., 1996](#) ; [Yamada et al., 2001](#) ; [Tsukasaki et al., 2003](#) ; [Takasaki et al.,](#)

[2010](#)). Although a phase 3 study in Japan demonstrated that the chemo-intensive LSG15 regimen was better than CHOP in newly diagnosed acute, lymphoma, or unfavorable chronic ATL, the CR rate was less than 20% for patients with acute ATL who received the LSG15 regimen and their 4 year survival was less than 10% ([Tsukasaki et al., 2007](#)). In the United States, a meta-analysis study including 195 ATL patients treated with modern therapies between 2000 and 2016, showed that the median survival rate was 4 months for acute ATL, 10 months for ATL lymphoma, 72 months for chronic/smoldering ATL, and not reached for unfavorable chronic type, with 4-year survival rates of 10, 4, 60, and 83%, respectively ([Malpica et al., 2018](#)). Overall, chemotherapy improved response rates in lymphoma but not in acute subtypes, yet with little impact on long-term survival.

Indolent smoldering or chronic ATL subtypes have a better prognosis than the aggressive ATL subtypes ([Shimoyama, 1991](#)). These variants were classically managed in Japan by a watchful-waiting policy ([Takasaki et al., 2010](#)), until progression of the disease or with chemotherapy when poor prognostic factors were identified ([Tsukasaki et al., 2009](#)). In a study of watch and wait for indolent ATL in Brazil over 14 years, the reported overall survival rates remained less than 20% at 5 years in both types ([Bittencourt et al., 2007](#)). Longer follow ups in Japan using this policy, showed that patients with smoldering ATL had an estimated 15-year survival rate of 13% with a median survival of 3 years, whereas patients with chronic ATL had an estimated 15-year survival rate of 15% with a median survival of 5 years ([Takasaki et al., 2010](#)). Thus, watch and wait strategy or treatment of the

smoldering and chronic subtypes with chemotherapy still associate with a poor long-term outcome.

Important advances in the treatment of ATL were reported with the combination of two antiviral agents: AZT and IFN, which induced a high rate of response and became a standard treatment of ATL ([Gill et al., 1995](#); [Hermine et al., 1995](#); [Bazarbachi and Hermine, 1996](#); [Kchour et al., 2009](#); [Bazarbachi et al., 2010](#), [2011](#); [Malpica et al., 2018](#)). The efficacy of this combination was confirmed, with minor differences, in various clinical trials and in a worldwide meta-analysis ([Matutes et al., 2001](#); [White et al., 2001](#); [Hermine et al., 2002](#); [Ratner et al., 2009](#); [Bazarbachi et al., 2010](#)). These results have transformed the clinical management of ATL in most parts of the world ([Bazarbachi et al., 2010](#), [2011](#); [Kinpara et al., 2013](#)). Indeed, AZT/IFN proved highly effective and significantly improved survival in the leukemic chronic and smoldering subtypes of ATL as well as in a subset of the acute subtype with wild type P53 ([Bazarbachi et al., 2010](#)). Patients with the lymphoma subtype benefited from induction chemotherapy, when given simultaneously or sequentially with AZT and IFN ([Hodson et al., 2011](#)). Patients with previously untreated ATL or newly diagnosed ATL achieved higher response rates ([Matutes et al., 2001](#); [Hermine et al., 2002](#)) compared to heavily treated patients ([White et al., 2001](#)). An ongoing randomized trial in Japan is testing AZT and IFN versus watchful waiting in patients with indolent ATL. Unfortunately, many patients are either resistant or progress even after a long period of disease control. Furthermore, treatment should be continued for life as relapse always occurs upon stopping therapy, indicating that AZT/IFN is not curative. In the United

States, first-line AZT/IFN resulted in a median progression-free survival (PFS) in patients with aggressive ATL who achieved CR after AZT/IFN of 48 months versus 11 months after chemotherapy ([Malpica et al., 2018](#)), suggesting that AZT/IFN can be used against aggressive ATL, as up-front option followed by chemotherapy switch in non-responders. At the molecular level, this combination inhibited the reverse transcriptase activity and modified the clonality pattern in responding ATL patients ([Macchi et al., 2017](#)). Since reverse transcriptase mediated viral replication does not occur in the malignant cells, these results highly suggest that the primary target of the AZT/IFN combination is the ATL microenvironment, specifically *de novo* infection of T cells by HTLV-1 which appears critical for the survival of the malignant clone.

Because of the high rate of relapse after conventional chemotherapy, allogeneic stem cell transplantation (alloSCT) is an attractive potentially curative option ([Iqbal et al., 2019](#)). However, most of the reports on alloSCT are from Japan. Large retrospective Japanese studies and a smaller European report demonstrate that alloSCT results in long-term survival in roughly one third of transplanted patients but only a small percentage of patients can make it to transplant ([Hishizawa et al., 2010](#) ; [Bazarbachi et al., 2014](#)).

Overall, current treatments of aggressive ATL subtypes are not satisfactory. Indeed, patients with acute and lymphoma subtypes who do not respond to primary therapy remain a population with unmet medical need. The lack of curative therapy of ATL, and the low survival rates in ATL patients inquire

exploring new targeted therapies to improve survival and achieve cure for these patients.

Innovative Therapies of Adult T Cell Leukemia

Monoclonal Antibodies

Mogamulizumab

C-C chemokine receptor 4 is a chemokine receptor known to be selectively expressed in type 2 helper T cells (Th2 cells) and regulatory T cells (T_{reg}) ([Ishida and Ueda, 2006](#)). CCR4 is involved in leukocyte migration and is expressed on ATL cells. Mogamulizumab (KW-0761) is a humanized defucosylated monoclonal antibody targeting CCR4 ([Ishii et al., 2010](#) ; [Subramaniam et al., 2012](#) ; [Tobinai et al., 2012](#)). Interestingly, Mogamulizumab exhibits its antitumor activity in ATL by various mechanisms of action. Studies have shown that this drug induces a depletion of T_{reg} leading to an increased antitumor immune response ([Sugiyama et al., 2013](#) ; [Ni et al., 2015](#)). In addition, it highly increases antibody-dependent cellular cytotoxicity because of its reduced fucose ([Shinkawa et al., 2003](#) ; [Ishii et al., 2010](#)). In Japan, this drug is approved for treatment of patients with different T cell malignancies such as relapsed/refractory (R/R) CCR4⁺ ATL and cutaneous T-cell lymphoma (CTCL) ([Ishii et al., 2010](#)). The efficacy of Mogamulizumab was tested in 28 patients with relapsed ATL ([Ishida et al., 2012](#)). The overall response rate (ORR) was 50% with 8 CR and 5 PR, and the OS was 13.7 months ([Ishida et al., 2012](#)). Similarly, Mogamulizumab showed an efficacy in Phase I study for R/R ATL and peripheral T-cell lymphoma (PTCL) in Japan with a response rate of 31% ([Makita and Tobinai,](#)

[2017](#)), and in a randomized Phase II study conducted on R/R patients in the United States and Europe ([Makita and Tobinai, 2017](#), reviewed in [Hermine et al., 2018](#)). Mogamulizumab also improved response rate in newly diagnosed ATL patients when combined to dose-intensified chemotherapy but failed to improve progression free and overall survival ([Ishida et al., 2015](#)).

Anti-CD25 Antibodies

Adult T cell leukemia cells are known to express CD25, the alpha chain of the human IL-2. Thus, the efficacy of naked or Yttrium-90 anti-CD25 antibody was tested yielding few CR in indolent subtypes ([Waldmann et al., 1993](#), [1995](#)). Daclizumab is another humanized monoclonal antibody targeting CD25 ([Berkowitz et al., 2014](#)). In ATL, a phase 2 clinical trial demonstrated that Daclizumab blocks IL-2 binding to CD25 on ATL cells. Thus, an effective clinical response was acquired, especially in patients with indolent ATL ([Berkowitz et al., 2014](#), reviewed in [Hermine et al., 2018](#)). This monoclonal was withdrawn from the market in March 2018.

Anti-transferrin Receptor Antibody

HTLV-1 infected cells were shown to constitutively express high levels of surface transferrin receptor. A24 is a monoclonal antibody directed against this receptor. Only pre-clinical studies were performed using this antibody. A24 induced apoptosis in both ATL cells and primary ATL cells from both acute and chronic ATL patients. Furthermore, A24 also inhibited (^{55}Fe)-transferrin uptake in activated T cells and blocked T-cell proliferation *in vitro* and *ex vivo* ([Moura et al., 2004](#)).

Anti-KIR3DL2 Monoclonal Antibody

KIR3DL2 (CD158K), a killer immunoglobulin-like receptor (KIR) normally expressed by a subset of natural killer (NK) cells is aberrantly expressed in Sezary syndrome and several other CTCLs ([Battistella et al., 2017](#)). In few ATL patients, circulating tumor cells may also express KIR3DL2 ([Obama et al., 2007](#)), a simple biomarker that identifies most acute-type ATL (Cheminant et al. unpublished data). It has been suggested that HTLV-1 may play a role in KIR3DL2 expression, combined to DNA methylation of the *KIR3DL2* gene promoter. Moreover, IPH4102, a monoclonal antibody directed against KIR3DL2 that has shown beneficial clinical activity in relapsed CTCL patients ([Bagot et al., 2019](#)), can selectively kill human KIR3DL2+ primary ATL cells *ex-vivo* (Cheminant et al. unpublished data).

Alemtuzumab

Alemtuzumab (Campath-1H) is a chimeric humanized antibody that binds to a glycoprotein (CD52), which is highly expressed on benign and malignant B and T- lymphocytes and monocytes ([Buggins et al., 2002](#)). Alemtuzumab showed an antitumor activity in various cancer types such as T-cell prolymphocytic leukemia and B-cell chronic lymphocytic leukemia ([Laribi et al., 2017](#)). In ATL, a phase 2 clinical study using Alemtuzumab in acute, chronic, and lymphoma subtypes resulted in an ORR of 52%, mostly in the blood, but unfortunately with a short duration of response ([Sharma et al., 2017](#) , reviewed in [Hermine et al., 2018](#)).

Brentuximab Vedotin

Brentuximab vedotin (BV or SGN-35), is an anti-CD30 monoclonal antibody, conjugated to a microtubule poisoning agent monomethyl auristatin E. The latter is a cytotoxic agent, released by proteolytic cleavage following binding to anti-CD30 expressing cells, responsible of cell death induction ([Laribi et al., 2018](#)). Brentuximab vedotin is approved for the treatment of many tumors such as Hodgkin lymphoma (HL), CD30⁺ PTCL, and CD30⁺ CTCL. Several clinical trials are currently being conducted on patients with R/R CD30⁺ lymphomas, including some ATL patients under a pilot study in patients with R/R disease (NCT01703949), and a phase 2 study on patients with R/R CD30-low mature T-cell lymphomas ([Hermine et al., 2018](#)). Importantly, the ECHELON 2 randomized trial demonstrated that front-line treatment with BV and chemotherapy is superior to CHOP for patients with CD30-positive PTCL as shown by a significant improvement in PFS and OS with a manageable safety profile ([Horwitz et al., 2019](#)).

Anti-PD-1 Antibodies

Genomic analysis has shown a higher mutation rate in ATL than in other hematopoietic cancers. These changes include the T-cell receptor, nuclear factor κ B, and immune surveillance pathways, including overexpression of the programmed cell death 1 ligand (PD-L1) gene. [Kataoka et al. \(2016\)](#) reported the genetic evidence of clonal selection of ATL cells by way of PD-L1 overexpression through disruption of its 3' untranslated region (UTR) in 16% of their cohort. Several phase 1/2 studies of nivolumab, an anti-PD-1 antibody, are ongoing. Among them, Ratner et al. reported rapid progression

of ATL in sequential three patients after the treatment ([Ratner and the Authors, 2018](#) ; [Ratner et al., 2018](#)), supporting for the probable role of PD-1 functioning as a tumor suppressor reported in a mouse model ([Wartewig et al., 2017](#)). However, the other group did not experience such progression, requiring further evaluation of anti-PD-1 antibodies for especially aggressive ATL with PD-L1 overexpression ([Ishitsuka et al., 2018](#)).

Lenalidomide

Lenalidomide, a thalidomide analog, is an immunomodulatory drug with pleiotropic mechanisms of action, involving anti-inflammatory, antiangiogenic, and antitumor effects (reviewed in [Kotla et al., 2009](#) ; [Ito and Handa, 2016](#) ; [Chamberlain and Cathers, 2019](#)). Lenalidomide was approved by the FDA for the treatment of multiple myeloma, mantle cell lymphoma, and myelodysplastic syndrome with deletion 5q. In addition, lenalidomide exhibited clinical activity in other malignancies including acute myeloid leukemia and non-Hodgkin lymphoma. Its immunomodulatory properties include augmentation of NK cell number and cytotoxicity, activation of T cells, and alteration of cytokine production by monocytes ([Kotla et al., 2009](#) ; [Ito and Handa, 2016](#)).

Clinical trials on lenalidomide monotherapy in ATL include a phase 1 dose-escalation study on Japanese patients with ATL and PTCL ([Ogura et al., 2016](#)). Lenalidomide safety, maximum tolerated dose, and efficacy were investigated in a small cohort study of 13 patients (9 ATL, 4 PTCL). A maximum tolerated dose of 25 mg daily on each day of 28-day cycle was recommended for phase 2 studies ([Ogura et al., 2016](#)). Subsequently, a multicenter phase 2 open-label study of 26 patients with relapsed/recurrent <https://assignbuster.com/novel-treatments-of-adult-t-cell-leukemia-lymphoma/>

ATL (15 acute type, 7 lymphoma type, and 4 chronic type) was conducted ([Ishida et al., 2016](#)). Lenalidomide demonstrated significant anti-leukemic activity, accompanied by a tolerable toxicity profile. Briefly, the CR and response rates were 19 and 42% respectively with a median overall survival of 20 months. This study resulted in the approval of lenalidomide for clinical use in Japan for treating R/R ATL patients in March 2017 ([Ishida et al., 2016](#)).

Recently, a case report by [Oka et al. \(2019\)](#) described a potential for low-dose lenalidomide in maintenance therapy of ATL. Briefly, daily treatment with low-dose lenalidomide (5 mg/day) following LSG15 chemotherapy with mogamulizumab maintained complete remission in a patient with acute ATL, whose condition remained stable with no recurrence for at least 24 months. Lenalidomide triggered an increase in the numbers of CD3⁺ CD8⁺ cytotoxic T cells, CD3⁺ CD4⁺ T cells and CD56⁺ CD16⁺ NK cells. This report warrants further investigations on possible promising combination of lenalidomide with monoclonal antibodies and chemotherapy in patients who are not eligible for HSCT. In fact, given that mogamulizumab antitumor activity completely depends on antibody dependent cellular cytotoxicity, mainly through NK cells, while lenalidomide augments NK cells activity and number, investigating a combination of both drugs in ATL treatment might result in favorable outcomes.

Arsenic Trioxide and Interferon-Alpha

Despite the important advances in the treatment of ATL using the combination of AZT/IFN many patients are either resistant or progress even

after a long period of disease control. Overall, the lack of curative therapy of ATL, in patients as well as in preclinical or naturally infected models ([Turpin et al., 2017](#)), underlies the importance of exploring new therapies targeting ATL leukemia initiating cells (LICs), to achieve disease eradication, rather than long term disease control. *In vitro* , the combination of arsenic trioxide (AS) and IFN selectively induces cell cycle arrest and apoptosis of ATL cells ([Bazarbachi et al., 1999](#)). This was associated with proteasome-mediated Tax degradation ([El-Sabban et al., 2000](#) ; [Nasr et al., 2003](#)). This AS/IFN combination cured Tax-driven murine ATL through LIC eradication and delayed tumor cell exhaustion ([El Hajj et al., 2010](#)). Critically, adding the proteasome inhibitor bortezomib (PS-341) essentially blocks the degradation of Tax triggered by the AS/IFN combination, and reversed the enhancement of survival in secondary and tertiary recipients in serial transplantation assays. Overall, ATL cells are addicted to continuous Tax expression for their LIC activity and long term proliferation but not for their short-term tumor growth ([El Hajj et al., 2010](#)).

A phase 2 trial involving seven patients with relapsed/refractory ATL showed that AS/IFN combination induced one complete remission and three partial remissions, with one patient who remained alive and disease free for more than 5 years ([Hermine et al., 2004](#) and unpublished). A prospective phase 2 study tested the efficacy, and safety of the combination of AS/IFN/AZT in 10 *de novo* chronic ATL patients ([Kchour et al., 2009](#)). Strikingly, AS/IFN/AZT therapy led to a 100% response rate and 70% complete remission rate (7 CR, 2 CR with 5% circulating atypical lymphocytes and 1 PR). Some patients exhibited a sustained response, even after treatment withdrawal, suggesting

a potential cure through ATL LICs loss ([Kchour et al., 2009](#)). Side effects were very moderate and mostly hematologic. Although these treated patients received a suboptimal 5-days-per-week treatment, 3 of 6 patients remained in continuous CR for 7–18 months after discontinuation of maintenance therapy, as compared to five patients with chronic ATL treated with AZT/IFN alone who all relapsed before 5 months ([El Hajj et al., 2010](#)). Recently, a clinical trial tested AS consolidation in nine patients with ATL (four patients with lymphoma, two patients with acute, and three patients with indolent ATL). Four patients were in CR, three patients were in PR, one patient in stable disease and the last one was in progressive disease. These patients received up to eight weeks of intravenous AS at the dose of 0.15 mg/kg/day intravenously in combination with AZT/IFN. One patient died rapidly, while the remaining eight patients showed prolonged median duration of response of 24 and 39 months from initiation of AS consolidation and from diagnosis, respectively ([Marcais et al., 2020](#)). These results suggest that consolidation with arsenic could be an option for ATL patients achieving a satisfactory response after induction therapy and who are not eligible for HSCT ([Marcais et al., 2020](#)).

Vaccines

Recent efforts suggested anti-ATL vaccines as a potential therapeutic option for ATL. These vaccines are meant to stimulate host immune response against the virus, and may provide some clinical benefits, especially for R/R ATL. A Tax peptide-pulsed dendritic cell (Tax-DC) vaccine was designed to augment Tax-specific cytotoxic T lymphocyte (CTL) response. This vaccine consists of autologous DCs pulsed with different Tax peptides known to be

the Tax-inducing CTL epitopes ([Suehiro et al., 2015](#)). A pilot clinical trial was performed on three previously treated ATL patients who were classified as intermediate to high risk patients ([Suehiro et al., 2015](#)), and led to favorable clinical outcomes. Indeed, two patients survived for more than 4 years after vaccination without severe adverse effects ([Kannagi et al., 2019a](#)). This Tax-DC vaccine is currently under a phase 1 trial, with a promising clinical outcome. This vaccine can represent a safe alternative maintenance therapy for ATL. It can also be applied in case of indolent ATL or might be a prophylactic approach in HTLV-1 carriers ([Kannagi et al., 2019b](#)).

Another therapeutic vaccine candidate for treatment of ATL, called THV02, comprises two lentiviral vectors to be used in a prime/boost regimen. This vaccine encodes for a peptide deriving from the viral proteins Tax, HBZ, p12I, and p30II. THV02 proved to induce a cellular response in animal models warranting conducting clinical trials to test its efficacy (reviewed in [Hermine et al., 2018](#)).

Epigenetic Therapies Against ATL

Ezh Inhibitors

Enhancer of Zeste Homolog 1 and 2 (EZH1 and EZH2) are polycomb repressive protein components (PRC). EZH2, the catalytic subunit of PRC2, mediates transcriptional silencing through trimethylation of histone H3 lysine 27 ($H_3K_{27}^{me3}$). Mutation or overexpression of EZH2 has been linked to numerous types of cancer and EZH2 inhibitors are being evaluated in clinical trials as potential anti-cancer agents (reviewed in [Lund et al., 2014](#) ; [Gan et](#)

[al., 2018](#); [Nakagawa and Kitabayashi, 2018](#)). More recently, significance of EZH1 has been recognized also ([Yamagishi et al., 2019](#)). In ATL cells, miR-31 level is epigenetically regulated, and aberrant upregulation of polycomb proteins including EZH1/2 contribute to miR-31 downregulation in an epigenetic fashion, leading to activation of NF- κ B and apoptosis resistance ([Yamagishi et al., 2012](#)). EZH2 is affected by the HTLV-1 Tax protein. Likewise, the Tax-dependent immortalized cells showed H₃ K₂₇^{me3} reprogramming that was significantly similar to that of ATL cells ([Fujikawa et al., 2016](#)).

Pharmacologic inhibition of EZH2, *in vitro*, in ATL cells resulted in reversed epigenetic aberrations and selective elimination of leukemic and HTLV-1-infected cells presenting EZH2 as possible target for epigenetic therapy in ATL ([Fujikawa et al., 2016](#)).

Valemetostat (DS-3201) is a potent selective dual inhibitor of EZH1 and EZH2 with antineoplastic potential especially in lymphomas including ATL ([Yamagishi et al., 2019](#)). A multicenter, Phase 1 multiple ascending dose study of DS-3201b in Japanese patients with R/R NHL including ATL was conducted to evaluate the safety, pharmacokinetics, and recommended dose of DS-3201. Based on the promising results, a phase 2 trial of valemetostat for R/R aggressive ATL after mogamulizumab treatment is ongoing in Japan.

Histone Deacetylase Inhibitors

Histone deacetylase inhibitors (HDACI) are anti-cancer drugs that relieve histone deacetylation imposed by HDAC resulting in chromatin remodeling

and reactivation of transcriptionally suppressed genes (reviewed in [Li and Seto, 2016](#)). Several HDACIs, vorinostat, romidepsin and belinostat, were FDA approved for the treatment of PTCL. These include Vorinostat (SAHA) and Romidepsin for CTCL. Vorinostat induced 30% response rates ([Olsen et al., 2007](#)), while Romidepsin induced 34% response rates ([Whittaker et al., 2010](#)). Combining valproic acid, a first generation HDACI, with AZT/IFN as a maintenance therapy was tested in 13 ATL patients ([Ramos and Lossos, 2011](#)). A decrease of clonal disease was observed by PCR, only in one patient. However, primary ATL cells from this patient showed an increased HTLV-I expression and induced apoptosis upon treatment with vorinostat. Thus, these results could be extrapolated to eliminate residual disease ([Afonso et al., 2010](#)).

In vitro, many HDAC inhibitors exhibited excellent anti-leukemic potential against HTLV-1 transformed or ATL-derived cell lines and primary ATL cells by blocking Notch pathway, decreasing NF- κ B, and promoting apoptosis ([Mori et al., 2004](#); [Nishioka et al., 2008](#); [Yu et al., 2015](#)). These include valproic acid, vorinostat, romidepsin, panobinostat, and entinostat ([Mori et al., 2004](#); [Nishioka et al., 2008](#)). An orally bioavailable HDACi, AR-42 reduced the proliferation of ATL cell lines by promoting apoptosis and histone hyperacetylation and enhanced the survival of NOD/SCID ATL mouse model ([Zimmerman et al., 2011](#)). Romidepsin as single agent prolonged survival in MT1 NOD/SCID mouse model ([Yu et al., 2015](#)). Combination of Romidepsin with anti CD25 depsipeptide resulted in prolonged survival of a Met-1 ATL murine model ([Chen et al., 2009](#)). Panobinostat, a HDACI, decreased in levels of factors involved in ATLL cell proliferation and invasion

such as CCR4, IL-2R and HTLV-1 HBZ-SI, a spliced form of the HTLV-1 basic zipper factor HBZ, and induced apoptosis in ATL cells via activation of a novel RAIDD-caspase-2 pathway ([Hasegawa et al., 2011](#)).

Clinical trials on HDAC included a phase 1 trial on combination of Alisertib (an Aurora kinase A inhibitor) and vorinostat in treating relapsed/recurrent Hodgkins lymphoma, B-cell non-Hodkin lymphoma, and PTCL ([Siddiqi et al., 2019](#)). Alisertib combined to vorinostat showed encouraging clinical activity with a manageable safety profile.

Chidamide, which is an orally bioavailable member of the benzamide class of HDACI, was approved by CFDA in China for treating relapsed/refractory PTCL as monotherapy with a recommended dose of 30 mg twice weekly (BIW) although the dose finding results were not conclusive (reviewed in [Zhang et al., 2019](#)). A phase 1 trial of chidamide in Japan for patients with R/R NHL including ATL revealed that MTD was 40 mg BIW and best overall response was noted in 40 mg BIW cohort (N = 7): 1 CR, 5 PR, 1 SD. Four of the partial responders were ATL patients (among total five patients). In the 30 mg BIW dose cohort, 4/6 patients had stable disease after the 1st cycle (reviewed in [Zhang et al., 2019](#)). Based on the promising results, a phase 2 trial of chidamide for R/R aggressive ATL after mogamulizumab treatment is ongoing in Japan.

Concluding Remarks

Adult T cell leukemia remains a challenging disease with no current satisfying therapy. Indeed, about 40% of the patients after allo-HSCT, and 10–20% of those after chemotherapy could be cured without treatment for

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more than 5 years. Indolent forms of the disease present a long-term survival following treatment with antiviral therapies. The aggressive forms of the disease remain an unmet medical need, with only a small number of patients who can achieve long-term survival either following CR on antiviral therapy or if they make it to intensive chemotherapy +/- allo-HSCT. Pilot studies with Tax vaccination are promising. Monoclonal antibodies alone or combined to chemotherapy improved response rates, yet with little effect, if any, on overall survival. The use of epigenetic inhibitors yielded promising preclinical and phase 1 results. Arsenic trioxide combined with IFA targets Tax for degradation and cures murine ATL through elimination of LIC activity. Clinical studies suggest that addition of arsenic to antiviral therapy, or as a consolidation therapy, may achieve disease eradication and long-term survival. Based on the progress in understanding the pathophysiology of ATL, and the risk-adapted treatment approaches to different ATL subtypes, future strategies should include new targeted therapies that take into account the host immune responses and the host microenvironment including HTLV-1 infected non-malignant cells. That might lead the prevention of ATL development among high-risk HTLV-1 carriers.

Author Contributions

All authors contributed to the writing of this review, each under his/her area of expertise and approved this version before its submission.

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Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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