



Adult T-Cell Leukemia: a Comprehensive Overview on Current and Promising Treatment Modalities

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Abstract

Purpose of the Review Adult T-cell leukemia (ATL) is an aggressive chemo-resistant malignancy secondary to HTLV-1 retrovirus. Prognosis of ATL remains dismal. Herein, we emphasized on the current ATL treatment modalities and their drawbacks, and opened up on promising targeted therapies with special focus on the HTLV-1 regulatory proteins Tax and HBZ. **Recent Findings** Indolent ATL and a fraction of acute ATL exhibit long-term survival following antiviral treatment with zidovudine and interferon-alpha. Monoclonal antibodies such as mogamulizumab improved response rates, but with little effect on survival. Allogeneic hematopoietic cell transplantation results in long-term survival in one third of transplanted patients, alas only few patients are transplanted. Salvage therapy with lenalidomide in relapsed/refractory patients leads to prolonged survival in some of them.

Summary ATL remains an unmet medical need. Targeted therapies focusing on the HTLV-1 viral replication and/or viral regulatory proteins, as well as on the host antiviral immunity, represent a promising approach for the treatment of ATL.

Keywords Human T lymphotropic virus type 1 · adult T-cell leukemia · Tax · HBZ · Regulatory proteins

Introduction

HTLV-1: Generalities and Associated Diseases

The human T-cell leukemia virus type 1 (HTLV-1) is the first oncogenic retrovirus associated with a human disease [89]. HTLV-1 infects between 10 and 20 million people

worldwide, and is endemic in several regions, including Southern Japan, the Caribbean islands, Central and Latin America, Romania, the Middle East particularly North-East Iran, Intertropical Africa, Melanesia, and Central Australia [2, 37, 90]. In North America and Western Europe, HTLV-1 is predominantly encountered in migrants from endemic areas [21, 43]. HTLV-1 is the causative agent of a spectrum of diseases including the aggressive adult T-cell leukemia (ATL), which will be the focus of this review [109], a chronic neurological disease called HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) [38, 87], and an array of inflammatory diseases including uveitis, dermatitis, arthritis, and bronchiectasis (reviewed in [37]).

HTLV-1 Regulatory Proteins, Tax and HBZ, and ATL Pathogenesis

In addition to the typical retroviral *gag*, *pol*, and *env* structural genes, HTLV-1 genome encodes for several accessory and regulatory proteins that contribute to its pathogenesis. Regulatory proteins include Tax, Rex, p12, p13, p21, and p30, and are encoded by various open reading frames located in the pX region, at the 3' end of the HTLV-1 genome (reviewed in [6, 73]). The minus strand of the pX region

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produces an antisense transcript encoding the HTLV-1 basic leucine zipper protein (HBZ) regulatory protein [36, 73]. Among all described regulatory proteins, Tax and HBZ were heavily studied and are largely linked to HTLV-1 pathogenesis (reviewed in [39, 67, 74, 101]).

Tax is a multifaceted oncoprotein whose expression modulates multiple cellular functions including activation of transcription factors, inhibition of apoptosis, genetic instability, and epigenetic changes (reviewed in [81]). Tax induces angiogenesis and facilitates tumor cell extravasation, a hallmark of ATL [12, 33]. Post-translation Tax modifications control many of its functions such as NF- κ B activation [65, 66, 80]. Tax expression induces the oligoclonal expansion of HTLV-1-infected cells, playing a critical role in ATL initiation and leukemogenesis [75, 124]. Although Tax protein is not detected in most ATL cells, ATL-derived cells are addicted to Tax expression [24]. Importantly, a very small percentage of ATL-derived cells exhibit sporadic bursts of Tax expression, a critical event necessary for the maintenance and survival of the whole malignant population [70]. A number of studies established Tax as a potent oncoprotein driving ATL progression *in vitro* [95, 111] and *in vivo* (reviewed in [76]). Indeed, different *tax* transgenic mouse models led to distinct tumors and/or inflammatory lesions depending on the used promoter to drive Tax expression [41, 82, 94]. *tax* transgenic mice expressing Tax develop leukemia with striking ATL-like features that recapitulate the human disease [28, 44]. In a *Drosophila melanogaster* fly model, Tax expression resulted in a constitutive activation of NF- κ B and in a rough eye phenotype, indicative of cell transformation [102]. Finally, Tax-immortalized PBMC exhibited genetic and epigenetic profiles similar to those of HTLV-1-infected and ATL cells [3, 34].

Tax is a highly immunogenic protein and HTLV-1-infected cells minimize its expression to escape from the host immunity [56, 58]. Indeed, Tax-expressing cells are a major target of cytotoxic T-cells *in vivo* [5, 42]. During HTLV-1 infection, HBZ counteracts Tax overexpression to evade host immune response [8]. In a *Drosophila melanogaster* fly model, HBZ expression in *tax* Tg flies prevents Tax-induced NF- κ B hyperactivation, deterring malignant cellular proliferation and its subsequent senescence [4•]. Unlike Tax whose expression is often difficult to detect in ATL cells, HBZ is constitutively expressed in most HTLV-1-infected and ATL cells [73].

Different properties of these viral proteins may substantiate the difference in the corresponding *in vivo* phenotypes. In that sense, Tax-mediated activation of both canonical and non-canonical NF- κ B pathways enhances HTLV-1-induced proliferation and is critical for cellular transformation, but its hyperactivation, if left unrestrained, can be detrimental to infected cells and triggers cellular senescence [135]. HBZ antagonizes this function of Tax [134] and halts the

canonical NF- κ B activation [135]. Hence, HBZ-mediated inhibition of Tax functions diminishes immune and inflammatory responses [134] and enables cells to escape senescence [4•, 135].

The proliferative capacity of ATL cells is also partly due to interleukin-10 (IL-10) and its downstream signaling [97]. Indeed, newly diagnosed ATL patients exhibited high levels of IL-10 associated with an immunosuppressive profile [57, 64]. Both Tax [31•] and HBZ [130] promote the production of IL-10, which may inhibit the host antiviral immune response.

Adult T-Cell Leukemia: Clinical Characteristics, Classification, and Prognosis

ATL was first reported in Japan in 1976 [109]. It occurs in 1 to 5% of the infected individuals, after a very long latency period which sometimes surpasses 50 years (reviewed in [7]). ATL malignant cells carry a mature activated T-cell phenotype generally CD3⁺ CD4⁺ CD5⁺ CD7⁻ CD8⁻ CD25⁺. Variability in clinical presentation of ATL has led to the Shimoyama classification into four clinical subtypes: acute, lymphoma, chronic, and smoldering [100]. This classification relies on the sites of organ infiltration, presence/absence and degree of leukemic manifestation, as well as hypercalcemia and high lactate dehydrogenase (LDH) levels [30, 100].

Briefly, acute ATL displays a rapidly progressive clinical course, and accounts for 55–60% of patients. The clinical features include hepatosplenomegaly, systemic lymphadenopathy, skin lesions, hypercalcemia, high LDH, major lymphocytosis made of atypical cells with convoluted nuclei “flower cells,” and infiltration by leukemic cells of various organs including the central nervous system and the gastrointestinal tract, among others. Lymphoma ATL accounts for around 20–25% of patients, and exhibits the same symptoms as the acute subtype, but differs by the absence of lymphocytosis with less than 1% leukemia cells in the peripheral blood. Smoldering ATL accounts for 5–10% of cases and exhibits an indolent clinical course with normal leukocyte count and only a small percentage of leukemic flower cells, potential skin and lung involvement, lack of hypercalcemia, and normal LDH levels. Finally, chronic ATL accounts for 10–20% of patients and is characterized by high leukocytosis, lymphadenopathy, hepatosplenomegaly, normal to moderately elevated LDH levels, and absence of hypercalcemia or visceral involvement. The chronic ATL subtype is further divided into favorable and unfavorable subgroups, where the latter is mostly defined by high LDH levels, low serum concentrations of albumin as well as high serum urea concentration. Of note, “indolent ATL” refers to smoldering and “favorable” chronic subtypes, while the term “aggressive ATL” denotes the acute, lymphoma, and the “unfavorable” chronic subtypes. The aggressive forms are characterized by

an intrinsic chemo-resistance and a profound immunosuppression with associated opportunistic infections [13, 15, 100, 112], while the indolent subtypes are characterized by a better short-term prognosis, but a poor long-term survival [108].

Current and Promising Therapeutic Strategies for ATL that Are Not Targeting the Virus

ATL remains a challenging leukemia displaying the worst prognosis among all T-cell malignancies [122]. Even in recent years, the 5-year OS is estimated at 55, 31, 10, and 8% in the smoldering, chronic, lymphoma, and acute subtypes, respectively [61]. After more than four decades of research, the therapeutic management of ATL remains intricate. Several reasons dictate this challenge. ATL is distinct from most cancers which arise subsequent to the accumulation of somatic mutations. It is a virally induced leukemia where both viral proteins and the host immunity are implicated in the leukemogenesis. Attempts to tackle the leukemia by targeting leukemic cells with chemotherapy and monoclonal antibodies, without targeting the virus behind the leukemia, have failed and will likely continue to fail. In this review, we will provide a synopsis of the current management strategies of ATL including the watch-and-wait policy, conventional chemotherapy, allogeneic hematopoietic cell transplantation (allo-HCT), as well as the combination of two antiviral agents, zidovudine (AZT) and interferon-alpha (IFN) (reviewed in [15, 23, 118, 119••]) (Fig. 1A). We will also open up on potential anti-HTLV-1-targeted therapies of ATL with a special focus on two viral proteins, Tax and HBZ, as therapeutic targets (Fig. 1A).

A- Watch-and-Wait Strategy for Indolent ATL

A curative treatment modality is still lacking in most ATL patients. The identification of the ATL subtype proved essential to decide on the treatment strategy. Indolent ATL (smoldering and favorable chronic) subtypes associate with a better short-term prognosis as compared to the aggressive subtypes [100], and were historically managed through the “watch-and-wait” strategy [108]. Indeed, patients received chemotherapy only when the disease progressed [118]. A study conducted in Brazil over 14 years reported that the 5-year overall survival of indolent ATL patients under watch-and-wait policy was below 20% [18]. In Japan, the 15-year survival rate was 13% and 15% for smoldering and chronic ATL subtypes and the median survival of these patients was 3 and 5 years, respectively [108]. Thus, the watch-and-wait strategy allies with a poor long-term outcome [108] suggesting that patients with indolent ATL must be treated.

B- Supportive Care

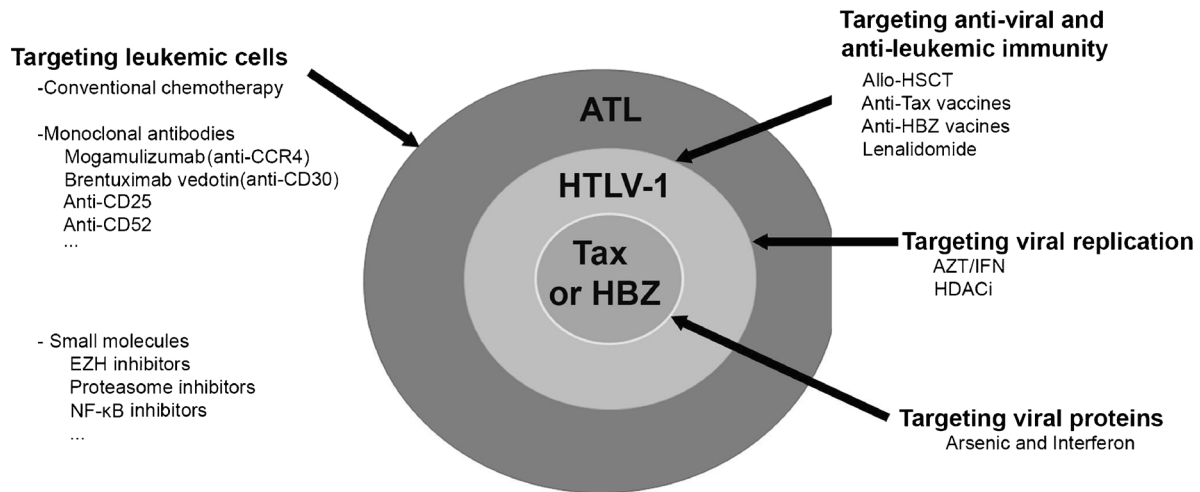
ATL patients are immunocompromised and may develop a variety of opportunistic infections, including cytomegalovirus or *Pneumocystis carinii* pneumonias, malignant strongyloidiasis, disseminated cryptococcosis or toxoplasmosis, disseminated fungal infections, as well as bacterial abscesses and sepsis [19, 121]. Thus, prophylaxis of these opportunistic infections is mandatory (reviewed in [15, 23, 118, 119••]). Similarly, intrathecal chemotherapy is recommended, particularly in aggressive ATL to prevent frequent CNS relapse.

C- Conventional Chemotherapy

In patients with aggressive ATL subtypes, Japanese trials used chemotherapy regimens inspired from acute lymphoblastic leukemia or non-Hodgkin lymphoma (NHL). Unfortunately, these adopted regimens had little effect on the survival of ATL patients, especially in the acute subtype [23, 27, 107, 108, 110, 114, 116, 127].

Six consecutive trials testing chemotherapy on ATL were conducted by the Japan Clinical Oncology Group [99, 115–117, 127]. The first regimen (LSG1 clinical trial) used VEPA (a combination of vincristine (VCR), cyclophosphamide (CPA), prednisolone (PSL), and doxorubicin (DOX)). ATL patients exhibited the lowest complete remission (CR) rate (18%) as compared to B-cell lymphoma (64%) and other non-ATL peripheral T-cell lymphoma (PTCL) (36%). Methotrexate was then added to VEPA in a phase III clinical trial (LSG2-VEPA-M). A better CR rate, as compared to LSG1-VEPA, was reached in ATL (37% versus 18%), although the highest CR rates were also achieved in patients with B-cell lymphoma and PTCL. It is worth noting that the median survival time (MST) of ATL patients enrolled in LSG1 or LSG2 was only 6 months and the 4-year OS rate did not exceed 8%. A third phase II clinical trial (JCOG870 or LSG4) was then tested on aggressive NHL including ATL. It consisted of three regimens VEPA-B-VCR, CPA, PSL, DOX, and bleomycin (BLM); M-FEPA-methotrexate (MTX), vindesine (VDS), CPA, PSL, and DOX; and VEPP-B-VCR, etoposide (ETP), procarbazine (PCZ), PSL, and BLM [115]. A higher CR was achieved in all patients as compared to LSG1/2. Yet, ATL patients still exhibited the worse CR rate as compared to B-cell lymphoma and PTCL, but a better CR rate as compared to ATL patients enrolled in LSG1/2 (43% versus 28%). The MST slightly increased from 6 to 8 months and the 5-year OS reached 12%. The failure of the three chemotherapy regimens to improve the OS of ATL patients prompted the Japanese groups to add pentostatin or 20-deoxycoformycin (DCF), an irreversible inhibitor of adenosine deaminase, to chemotherapy (VCR, DOX, ETP, PSL), under a phase II clinical trial (LSG 11

A



B

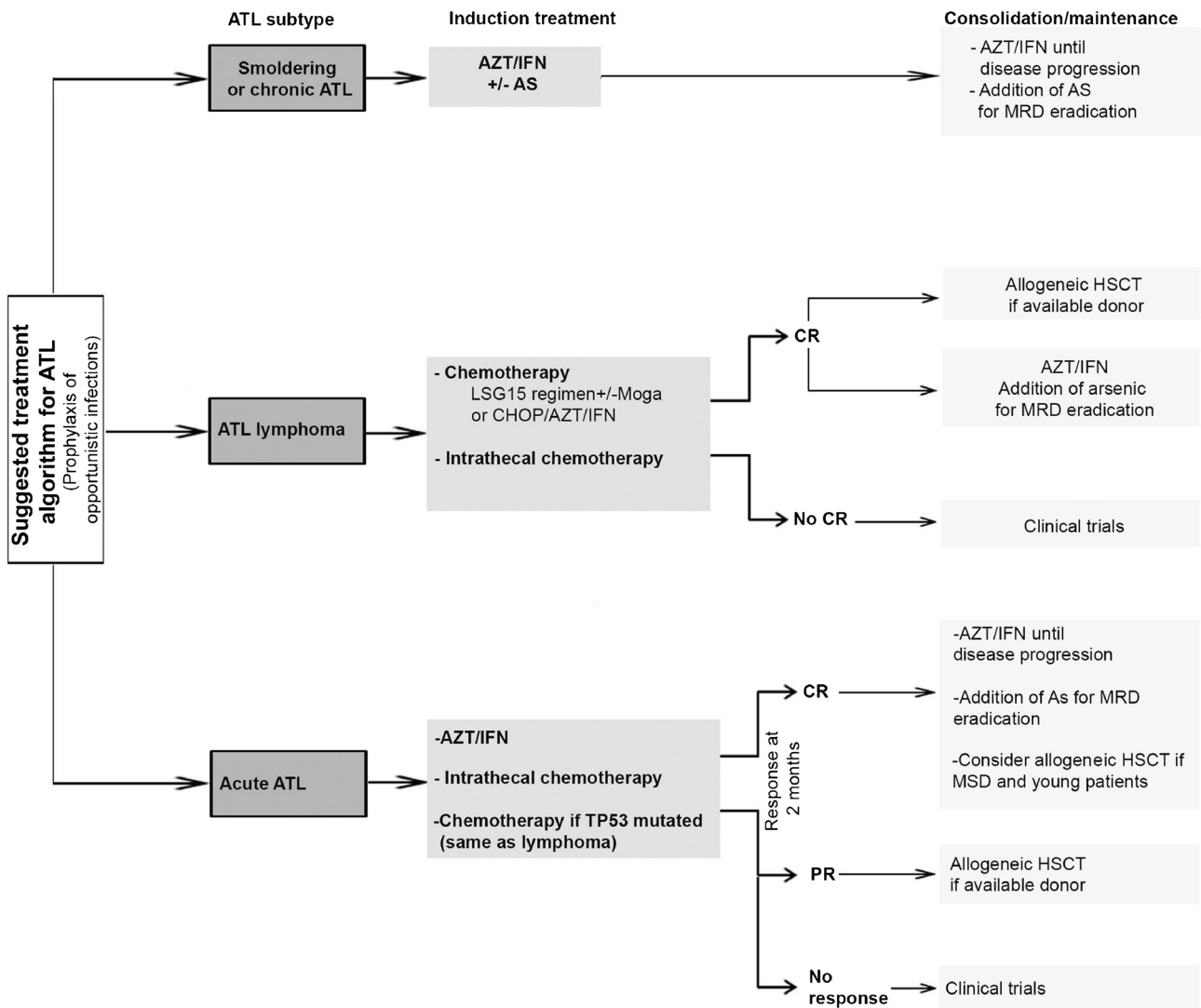


Fig. 1 **A** Current treatment modalities used to target ATL cells. **B** Suggested treatment algorithm for ATL

or JCOG9109). This study included exclusively untreated aggressive ATL patients [116]. CR was achieved in 17 out of 60 tested patients, but the MST and 2-year OS, after a median observation time of 27 months, were similar to those obtained under the LSG4 clinical trial. An intensive induction therapy supported by G-CSF was evaluated in 81 ATL patients [107]. The CR and response rates were 35.8% and 74.1%, respectively, but most patients relapsed and eventually died after a median survival of 8.5 months. Thereafter, a phase II clinical trial (LSG15 or JCOG9303) was conducted on newly diagnosed aggressive ATL patients (acute, lymphoma, and unfavorable chronic subtypes). It consisted of ranimustine (MCNU), VCR, CPA, DOX, PSL, VDS, ETP, and carboplatin (CBDCA) with MTX and PSL administered intrathecally, and the granulocyte colony-stimulating factor (G-CSF) was used prophylactically [127]. Overall, 33 and 42 patients out of 90 achieved CR and PR, respectively. The MST increased to 13 months and the 2-year OS rates reached 31%, making the regimen the standard treatment for aggressive ATL in Japan. Accordingly, a randomized phase III clinical trial (JCOG9801) was initiated later and compared LSG15 with CHOP-14 (CPA, DOX, VCR, and PSL) [117]. Overall 23 CR and 18 PR were achieved in 118 patients, and the MST and 3-year OS rates reached 12.7 months and 24%, respectively. Despite the high toxicity of this regimen, this study demonstrated that the chemo-intensive mLSG15 is better than CHOP-14 for aggressive ATL. In the USA, 195 ATL patients (acute, lymphoma, chronic, and smoldering) were enrolled in a retrospective study. The median survival rates were 4, 10, and 72 months for acute, lymphoma, and chronic/smoldering ATL, and not reached for unfavorable chronic type, and the 4-year OS rates were 10, 4, 60, and 83%, respectively [71]. In subgroup analysis, intensive chemotherapy regimens led to better response rates in the ATL lymphoma but not the acute ATL subtype, but yielded overall very little impact on the long-term survival.

D- Monoclonal Antibodies

Different monoclonal antibodies (mAb)-targeted cell surface molecules expressed on ATL cells were tested in clinical trials [30, 84, 85, 119••]. These mAb mostly targeted CCR4, CD25, CD30, CD52, and the surface transferrin receptor known to be overexpressed on ATL cells [51, 113, 123] [20, 78]. Mogamulizumab, a humanized monoclonal antibody, was used to target CCR4 [113], a chemokine receptor expressed on ATL cells. Phase I/II clinical trials proved the efficacy of mogamulizumab in patients with relapsed/refractory (R/R) CCR4⁺ ATL [53]. In newly diagnosed ATL patients, mogamulizumab combined to dose-intensified chemotherapy improved response rates particularly in the peripheral blood, but failed to improve progression-free survival (PFS) and OS [54]. A recent phase II randomized

study evaluated the efficacy and safety of mogamulizumab in 71 relapsed/refractory ATL patients as compared to the investigator choice [88]. Overall response rate was 11% and 0% in the mogamulizumab ($n=47$) and chemotherapy arms ($n=24$), respectively. Median duration of response in the mogamulizumab arm was 5.65 months. Despite some improvement of response, mostly in the blood compartment, PFS was quite disappointing (median PFS was 0.93 and 0.88 months in the mogamulizumab and investigator's choice arms, respectively) [88].

The efficacy of an anti-CD25 antibody was tested in indolent ATL and yielded some clinical response [123]. Alemtuzumab (Campath-1H), a chimeric humanized antibody that binds to the CD52 glycoprotein, resulted in promising overall response rates in acute, chronic, and lymphoma ATL, but only with a short duration of response ([98]. A24 mAb directed against the surface transferrin receptor induced apoptosis of ATL cell lines or primary ATL cells [20, 78] but this was not yet tested in patients. Brentuximab vedotin (BV), an anti-CD30 monoclonal antibody, was used in several clinical trials including patients with R/R CD30⁺ ATL patients (NCT01703949). Finally, nivolumab, an anti-PD-1 antibody, was investigated in several phase I/II clinical trials but unfortunately led to a rapid progression of ATL [92].

E- Targeting the Epigenetic Machinery

Tax modulates the expression of enhancer of zeste homolog 2 (EZH2) leading to H3K27me3-dependent reprogramming of around half of cellular genes [34]. Overexpression of Tax or HBZ increases the polycomb repressive complex 2 (PRC2) activity and both proteins directly interact with the PRC2 complex core components. Thus, targeting the epigenetic machinery was tested in ATL.

Primary ATL cells were sensitive to treatment with 3-deazaneplanocin A (DZNep), an EZH2 inhibitor, presenting EZH2 as a potential target for epigenetic therapy in ATL [96]. The transcription of miR-31, which negatively regulates the non-canonical NF- κ B pathway, is epigenetically silenced in ATL cells, due to the aberrant overexpression of EZH2 [128]. Pharmacological inhibition of EZH2 by a specific inhibitor, GSK126, reversed epigenetic aberrations and resulted in apoptosis of HTLV-1-infected and ATL cell lines [34]. In vitro pharmacologic inhibition of EZH2 resulted in reversed epigenetic aberrations and selective elimination of leukemic and HTLV-1-infected cells [34].

A multicenter phase I study of Valemostat (DS-3201), a potent selective dual inhibitor of EZH1 and EZH2, proved potent in lymphomas including ATL [129]. A phase II trial of Valemostat for R/R aggressive ATL is ongoing. Altogether, these studies demonstrate the role of epigenetics in modulating the epigenetic machinery and highlight the potential of epigenetic treatment strategies in ATL.

What Else to Target for ATL Therapy? Antiviral and Antileukemic Immunity, Targeting Viral Replication, and Regulatory Proteins

Antiviral and Antileukemic Immunity

Allogeneic Hematopoietic Cell Transplantation (Allo-HCT) Despite slightly improved outcomes with chemotherapy in newly diagnosed aggressive ATL, particularly in the lymphoma subtype [117] [71], chemotherapy alone has little effect on long-term survival, specifically in the acute subtype [15, 119••]. In light of the high rate of relapse after conventional chemotherapy, allo-HCT became an attractive therapeutic option to reach potential cure [52], and is currently adopted mostly for young patients with aggressive ATL. Numerous retrospective studies of allo-HSCT in ATL patients reported a relatively favorable outcome [35, 49, 60, 120]. Allo-HSCT results on more than 2000 ATL Japanese patients [35, 49, 60, 120], and from the European Society for Blood and Marrow Transplantation (EBMT), Lymphoma Working Party [16] reported similar promising results with long-term survival in around one third of transplanted patients [16, 49]. A clear evidence for graft versus ATL effect was documented including following donor lymphocyte infusion [131]. As a result, allo-HCT is currently recommended for transplant-eligible patients with aggressive ATL [23]. Yet, only a small percentage of ATL patients (around 10%) can make it to transplant and hence allo-HCT cures less than 5% of aggressive ATL patients.

Lenalidomide Lenalidomide is an immunomodulatory drug used in the treatment of several hematological malignancies such as multiple myeloma and NHL. Lenalidomide demonstrated a significant anti-ATL activity and a tolerable toxicity profile in a multicenter phase II open-label study of patients with relapsed/recurrent ATL [55]. This resulted in the approval of lenalidomide for treating R/R ATL patients in Japan. Recently, low-dose lenalidomide (5 mg/day) was proposed as a maintenance therapy of ATL, following intensive chemotherapy combined with mogamulizumab. This maintenance therapy resulted in continuous complete remission in one patient with acute ATL lasting more than 24 months [85].

Anti-Tax or Anti-HBZ Vaccines Vaccination approaches for ATL therapy mostly target Tax, HBZ, or both. In that sense, a Tax peptide-pulsed dendritic cell (DC) vaccine was designed to augment Tax-specific CTL response. This vaccine consists of autologous DCs pulsed with different Tax peptides known to be the Tax-inducing CTL epitopes [104]. A pilot clinical trial led to favorable clinical outcomes [104]. Two patients survived for more than 4 years after

vaccination [59]. A recombinant vaccinia virus (rVV) that induced an HBZ-specific T-cell response improved the survival of HBZ-induced lymphoma-challenged mice [105]. THV02, comprising two lentiviral vectors to be used in a prime/boost regimen, encodes for a peptide deriving from the viral proteins Tax, HBZ, p12I, and p30II and represents another vaccine candidate for treatment of ATL. THV02 induced a promising cellular response in animal models warranting conducting clinical trials to test its efficacy in patients (Hermine et al. personal communication).

Targeting Viral Replication

Zidovudine (AZT) and Interferon-Alpha (IFN) A main distinguishing feature of ATL is the presence of the HTLV-1 retrovirus. Thus, early attempts of targeted therapy of ATL used the combination of two antiviral agents: AZT and IFN [9, 14, 15, 30, 40, 46, 47, 62, 68, 71, 75, 93, 125]. Newly diagnosed ATL patients attained higher response rates using this combination [47, 75] compared to heavily treated patients [125]. In a worldwide meta-analysis that included more than 250 patients with ATL, first-line treatment with AZT/IFN improved the 5-year OS (46% compared to 14% after chemotherapy) [14]. Similarly, first-line treatment with AZT/IFN improved median PFS in patients with aggressive ATL (48 months versus 11 months after chemotherapy) [71]. High doses of both agents should be used and must be maintained for 1 to 2 months despite cytopenia. The smoldering and chronic subtypes benefited most from this antiretroviral therapy with a significant prolongation of survival (100% at 5 years) [14]. As a result, AZT/IFN became the standard treatment of indolent ATL in most parts of the world [14, 15, 23, 30, 68, 71, 118]. In Japan, an ongoing randomized clinical trial is comparing the watchful waiting strategy and AZT/IFN treatment in patients with indolent ATL.

Similar encouraging results were obtained in a subset of acute ATL patients who achieved CR after AZT/IFN [14]. A wild-type TP53 predicts response to AZT/IFN [25] and hence TP53 mutation status should be tested in newly diagnosed acute ATL patients. In the lymphoma subtype, treatment with AZT/IFN alone yielded very poor results [14] but significant improvement of OS was achieved when induction chemotherapy was given simultaneously or sequentially with AZT and IFN [50]. In the USA, first-line treatment of aggressive ATL who achieved CR with AZT/IFN resulted in a median progression-free survival (PFS) of 48 months (versus 11 months after chemotherapy) [71], suggesting that AZT/IFN can be used against aggressive ATL, as an up-front option followed by chemotherapy switch in non-responders. At the molecular level, AZT/IFN inhibits the reverse transcriptase activity and modifies the clonality pattern in responding ATL patients [11, 69, 81].

Unfortunately, despite this encouraging improvement in OS particularly in the indolent subtypes of ATL and a fraction of acute ATL, many patients remain resistant, and even in those who responded, the disease progresses after treatment interruption even after a long period of disease control. Indeed, AZT/IFN should be continuously administered to prevent the relapse, which always happens upon stopping therapy, indicating that AZT/IFN is not curative. Overall, patients with acute and lymphoma ATL remain an unmet medical need condition.

Histone Deacetylase Inhibitors (HDACi) Several HDAC inhibitors including valproic acid, vorinostat, romidepsin, panobinostat, entinostat, and AR-42 proved efficient in vitro against HTLV-1-transformed or ATL-derived cell lines and primary ATL cells [22, 45, 77, 83, 132, 136]. Clinically, vorinostat and romidepsin induced around 30% response rates in PTCL [86, 126]. Importantly, the HDAC inhibitor panobinostat induced apoptosis in ATL cells [45]. Additionally, sodium valproate (VPA) strongly impaired the expression of HBZ [17]. HBZ downregulation increased Tax mRNA levels over time, suggesting that VPA reversed the epigenetic control over Tax expression, thereby exposing latently HTLV-1-infected cells to the immune system [17]. VPA was also tested in combination with AZT/IFN as a maintenance therapy on 13 ATL patients [91], of which only one patient exhibited a decrease of the clonal disease [1]. A phase 1 clinical trial combining an Aurora kinase A inhibitor, Alisertib, with vorinostat yielded promising clinical activity in treating relapsed/recurrent Hodgkin's and NHL, as well as PTCL [103]. Chidamide was approved by the CFDA in China for treating relapsed/refractory PTCL with 4/6 patients having a stable disease (SD) after the 1st cycle [133]. The same HDACi was tested in Japan, with a higher dose, in a phase 1 trial for patients with R/R NHL, and revealed a best overall response with 1 CR, 5 PR, and 1 SD out of 7 treated patients. The 5 PR were achieved in ATL patients [133]. A phase 2 clinical trial testing chidamide after treatment with mogamulizumab is currently ongoing in Japan for R/R aggressive ATL.

Targeting the Viral Regulatory Proteins

Because of the importance of Tax and HBZ in ATL development and maintenance of the leukemic phenotype, targeted therapy of ATL may implicate direct targeting of these viral proteins or indirect targeting through inhibiting their downstream cellular targets or inducing antiviral immunity as stated above.

The importance of Tax in initiating and maintaining ATL makes it an excellent druggable target. The combination of arsenic trioxide (AS) and interferon- α (IFN) selectively induced cell cycle arrest and apoptosis of ATL cells [10].

This was associated with a reversal of the constitutive activation of NF- κ B and delayed shutdown of cell cycle-regulated genes secondary to Tax degradation by the proteasome indicating the importance of Tax expression for ATL cell survival [26, 32, 79]. In preclinical mice models, AS/IFN cured Tax-driven murine ATL through leukemia-initiating cell (LIC) eradication [28]. Blocking AS/IFN-induced Tax degradation protects ATL LIC activity, further confirming that ATL cells are addicted to Tax expression for their LIC activity [29]. Recent evidence demonstrated that AS/IFN-induced abrogation of LIC activity requires IL-10 expression shutoff [31•]. Indeed, loss of IL-10 secretion by ATL cells drives production of inflammatory cytokines by the microenvironment, followed by natural killer (NK) cells and macrophages-mediated clearance of ATL cells [31•]. Accordingly, anti-IL-10 monoclonal antibodies significantly increased the efficiency of AS/IFN therapy [31•]. Treatment of murine ATL with the triple combination of AS, IFN, and anti-IL-10 monoclonal yielded a 6-month survival of around 80% of mice and significantly decreased LIC activity in serial transplantation assays [31•]. Overall, these results emphasize the potential sequential targeting of malignant ATL cells and their immune microenvironment and provide a strong rationale to test the therapeutic effect of AS/IFN and anti-IL10 combination in ATL patients.

At the clinical level, a phase 2 trial on patients with relapsed/refractory ATL showed that AS/IFN combination led to some responses ([48]. Strikingly, adding AS to AZT/IFN therapy led to a 100% response rate and 70% complete remission rate in newly diagnosed chronic ATL patients [63] with some patients exhibiting an enduring response, even after treatment withdrawal, suggesting a potential cure through ATL LICs loss. Used as consolidation therapy after AZT/IFN treatment, AS led to highly encouraging results with prolonged median duration of response of 24 months and 39 months from initiation of AS consolidation and from diagnosis, respectively [72••]. Altogether, these studies highlight the importance of targeting the ATL driver Tax, yielding abrogation of LIC activity, thus reaching cure in preclinical mouse models and long-term enduring responses in ATL patients.

Conclusion

ATL remains a challenging disease with dismal prognosis and no current satisfying therapy. Indolent ATL and a fraction of acute ATL exhibit a long-term survival subsequent to antiviral therapies (Fig. 1B). In aggressive ATL, one third of the patients undergoing allo-HCT and less than 10% of those who received chemotherapy could have disease control for more than 5 years. Aggressive ATL remains an unmet medical need. Monoclonal antibodies alone or combined

to chemotherapy improved response rates, alas with little effect, if any, on overall survival. Yet, ATL cure is still out of reach in most patients. Based on the progress in understanding the pathophysiology of ATL, and the risk-adapted treatment approaches to different ATL subtypes (Fig. 1), future strategies should include new therapies that target the main driver of ATL: the HTLV-1 virus. These targeted therapies should focus on viral replication and the viral regulatory proteins, their downstream cellular targets, as well as the host immune responses and the host microenvironment including HTLV-1-infected non-malignant cells, likely critical for the survival of the malignant clone.

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