Adv Ther (2018) 35:135–152
https://doi.org/10.1007/s12325-018-0658-4

REVIEW

A Review of New Findings in Adult T-cell Leukemia–Lymphoma: A Focus on Current and Emerging Treatment Strategies

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Received: November 1, 2017 / Published online: February 6, 2018

ABSTRACT

Adult T-cell leukemia–lymphoma (ATL), a rare and aggressive T-cell malignancy caused by human T-cell lymphotropic virus type 1 (HTLV-1), is associated with a poor prognosis. Evidence-based standard treatment options are lacking and outcomes are generally unsatisfactory, particularly for patients with relapsed or refractory disease. Continued research is contributing to changing treatment landscape as a number of existing and investigational agents are evaluated. We describe the epidemiology of HTLV-1 and ATL, discuss the biology behind the disease, review current treatment practices and guidelines, and provide an overview of emerging therapies in ATL, with a focus on those for relapsed or refractory disease.

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Keywords: Adult T-cell leukemia–lymphoma; Chemotherapy; Human T-cell lymphotropic virus type 1; Oncology; Relapsed/refractory disease; Targeted agents

INTRODUCTION

Adult T-cell leukemia–lymphoma (ATL) is a rare and aggressive peripheral T-cell neoplasm caused by human T-cell lymphotropic virus type 1 (HTLV-1) [1, 2]. ATL can present with diverse clinical features, but typically is associated with circulating leukemic cells, generalized lymph node swelling, hepatosplenomegaly, skin involvement, opportunistic infections, and hypercalcemia [3]. ATL generally has a poor prognosis, with shorter overall survival (OS) relative to other peripheral T-cell lymphomas (PTCLs) [4]. Factors contributing to poor outcomes include inherent chemoresistance and immunosuppression associated with ATL, particularly with aggressive forms [5]. Although progress has been made in understanding the biologic underpinnings of ATL, treatment outcomes generally remain unsatisfactory. Management of relapsed or primary refractory (R/R) ATL presents a particular challenge. The purpose of this review is to provide an overview of ATL (biology, epidemiology, diagnosis, and prognosis) and a brief review of current treatment guidelines, and to discuss emerging

therapies, with a focus on those that may serve as viable treatment options for R/R ATL. This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

HTLV-1 AND ATL

ATL is caused by the HTLV-1 retrovirus [1, 2]. HTLV-1 causes transformation and clonal expansion of T cells, in some cases resulting in ATL [6]. Leukemogenesis of ATL is believed to be a multistep process involving a number of factors, including viral, epigenetic, and constitutional and acquired genetic factors and events [7, 8].

It is estimated that at least 5–10 million individuals worldwide are infected with HTLV-1 [9]. Infection with the HTLV-1 virus is endemic in several regions, including southwestern Japan, some parts of the Caribbean, South America, some areas of intertropical Africa (such as South Gabon) and of the middle East (such as the Mashad region in Iran), isolated clusters in Australo–Melanesia, and Romania (the only known region in Europe) [9]. In the USA and Europe, infection is usually seen in people from, or in sexual partners of people from, endemic regions [9–11].

Most individuals infected with HTLV-1 remain asymptomatic carriers; the lifetime risk of developing ATL among HTLV-1 carriers is estimated at 3–5% [12]. Currently there is no established method to prevent progression to ATL in HTLV-1 carriers, although several risk factors have been identified, such as host susceptibility factors, laboratory markers, and viral markers (reviewed by Iwanaga et al. [10]). In particular, proviral load appears to be a useful marker [13]. High proviral load is associated with increased risk of aggressive ATL [14].

The epidemiology of ATL reflects its association with HTLV-1. The geographic distribution of ATL corresponds with that of HTLV-1 carriers, with high incidence rates of ATL in HTLV-1 endemic regions [10]. For example, ATL accounts for approximately 25% of PTCLs in Asia (primarily Japan) compared with 2% in North America and 1% in Europe [4]. A recent study reported that ATL accounts for 5.5% of non-Hodgkin lymphoma (NHL) in Peru, 0.5% in Chile, and 1.1% in Central and South America overall [15]. The onset of ATL generally occurs following a latency period of approximately 30–50 years after initial HTLV-1 infection that occurs in most of the cases following breast feeding; as such, the disease primarily affects adults [11, 16–18]. The age of onset of ATL varies somewhat by geographic region; patients in the Caribbean or South America (40–50 years) and in the USA (approximately 50 years) tend to have a younger age at diagnosis than patients in Japan (where median age at diagnosis has increased from approximately 53 years in the 1980s to 66 years in 2006–2007) [10, 11, 19]. Regional differences have also been observed in the gender distribution of ATL. There is a clear male predominance in Japan but not in Jamaica [20] and one study from the USA showed a substantial female predominance [21].

DIAGNOSIS AND PROGNOSIS

Diagnosis of ATL is determined by a combination of clinical presentation and morphologic/immunophenotypic features of the malignant cells, along with confirmation of HTLV-1 infection [17, 22]. Abnormal T cells characteristic of ATL have markedly polylobated nuclei with homogeneous and condensed chromatin, small or absent nucleoli, and agranular and basophilic cytoplasm [22]. The cells have a flower petal-like appearance and often express a CD3+ CD4+ CD5+ CD7− CD8− CD25+ immunophenotype [23]. ATL tumor cells are detected in peripheral blood or biopsy of affected organs [17]. At least 5% of circulating abnormal T lymphocytes are required for a diagnosis of ATL in patients without histologically proven tumor lesions [22].

ATL is classified into four subtypes based on the Shimoyama criteria; the acute and lymphoma subtypes are considered aggressive forms, while chronic and smoldering ATL have a more indolent course [24]. Generally, the aggressive disease types comprise the majority of ATL cases. For example, in Japan and Brazil,

the acute type accounts for 55–60% of cases, lymphoma 20–25%, chronic 10–20%, and smoldering 5–10% [24–26]. However, data from the International Peripheral T-cell Lymphoma Project showed that 87% of aggressive ATL cases were the lymphoma type (13% were acute type) [27], suggesting that the lymphoma type might be more frequent than expected. In addition, some data indicate that the distribution may differ in other geographic regions [19, 28, 29].

The clinical features of ATL vary by disease type [24]. Acute-type ATL presents with a large number of circulating leukemia cells, generalized lymphadenopathy, hepatosplenomegaly, lytic bone lesions, visceral lesions, skin involvement, and systemic symptoms resulting from organ involvement, hypercalcemia, or opportunistic infection [3, 17]. The lymphoma type presents with lymphadenopathy in the absence of circulating leukemic cells in the peripheral blood. Patients may present with skin lesions, lung lesions, hepatomegaly, splenomegaly, and hypercalcemia, but these manifestations may be less frequent compared with the acute type [3, 17, 24]. Chronic-type ATL is associated with chronic peripheral lymphocytosis for several years and may occasionally be associated with skin and lung involvement, lymphadenopathy, and hepatosplenomegaly; no associated hypercalcemia or infiltration of the CNS, gastrointestinal tract, or bones are seen, and lactate dehydrogenase levels are normal or only slightly increased (less than twice the upper limit of normal) [3, 17, 24]. Chronic-type ATL may further be subdivided into favorable and unfavorable subtypes, based on clinical parameters [serum albumin, blood urea nitrogen (BUN), and lactate dehydrogenase (LDH) levels] [30]. The smoldering type characteristically shows skin or lung infiltration with no other visceral involvement, a normal lymphocyte count, and at least 5% abnormal lymphocytes in the peripheral blood [3, 17, 24]. Aggressive ATL types are associated with a particularly poor prognosis (median OS approximately 6–10 months); indolent types generally have a median OS of at least 2 years [19, 24, 25].

In addition to ATL disease type, several other prognostic factors have been identified. Recent evidence suggests there may be a higher frequency of poor prognostic factors among Caribbean patients compared with Japanese patients [31]. Factors that predict poor prognosis include poor performance status, elevated LDH level, at least four total involved lesions, hypercalcemia, age at least 40 years, thrombocytopenia, eosinophilia, bone marrow involvement, high interleukin-5 serum level, C–C chemokine receptor 4 (CCR4) expression, lung resistance-related protein, p53 mutation, and p16 deletion [22]. Risk models incorporating combinations of these factors have been developed that have shown utility in predicting outcomes [19, 27, 32, 33] and may provide further insight with regard to prognosis and/or treatment selection.

CURRENT TREATMENT LANDSCAPE

Currently, there are no optimal standard treatment regimens for ATL. Most patients with ATL do not achieve a cure with current treatment options [3] and the efficacy of long-term therapy is limited [34]. Enrollment in clinical trials is commonly recommended, particularly for patients with R/R ATL, for whom existing treatment options are quite limited [3, 22, 34].

Consistent with the geographic distribution of HTLV-1 and ATL, most of the existing clinical trial data in ATL are based on studies conducted in Japan. Thus, the data must be extrapolated to predict responses in Western patients. Evidence of regional differences in ATL (e.g., distribution of ATL disease types [19, 24–26, 28] and frequency of poor risk factors [31], as mentioned earlier) suggests the possibility of differences in treatment outcomes for different populations. Further, differences in outcomes between clinical trials conducted in the USA [35, 36] and those conducted with similar regimens in Japan suggest that ATL may be more chemoresistant in the Western hemisphere. Ongoing clinical studies in Western patients will add much needed efficacy/safety data in this population, which may help to further refine treatment selection. In addition, studies of molecular events associated with HTLV-1 transformation to ATL in different populations will help to

delineate these differences. However, it is important to note that most of the long-surviving patients in large series from Japan received allogeneic bone marrow transplantation [25].

Treatment strategies for ATL are based primarily on disease type, along with other prognostic factors and response to initial treatment [22, 34, 37]. In general, current treatment options for ATL include watchful waiting, zidovudine plus interferon-alfa (AZT/IFN), multi-agent chemotherapy, or allogeneic hematopoietic stem cell transplantation (allo-HSCT) [22, 34, 37]. Multi-agent chemotherapy may include the following combinations: CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone); CHOEP (cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone); dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin); hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone); or VCAP-AMP-VECP (vincristine, cyclophosphamide, doxorubicin, and prednisone; doxorubicin, ranimustine, and prednisone; and vindesine, etoposide, carboplatin, and prednisone). The selection of specific agents or combinations may vary by geographic region.

For first-line therapy, some international and US-based guidelines recommend the following approaches [22, 34, 37]. For chronic or smoldering ATL, observation may be appropriate for patients who are asymptomatic. Patients who are symptomatic (e.g., skin lesions, opportunistic infections) may be treated with skin-directed therapies or antiviral therapy (AZT/IFN), or may consider participation in a clinical trial. For unfavorable chronic or acute ATL, enrollment in a clinical trial is recommended; alternatively, treatment options include AZT/IFN or combination chemotherapy (e.g., CHOP, CHOEP, dose-adjusted EPOCH, hyper-CVAD, or VCAP-AMP-VECP). However, for chronic ATL, studies have shown that chemotherapies may worsen the prognosis when compared to watch and wait [38], whereas in the same situation, AZT/INF may induce long-term survival [29]. For the lymphoma subtype, enrollment in a clinical trial is again recommended; alternatively, patients may receive treatment with combination chemotherapy (as mentioned for acute ATL). In some cases, particularly in Japan, the mLSG15 regimen (VCAP-AMP-VECP) is recommended for aggressive ATL (i.e., acute or lymphoma subtype) [22, 39]. Similar regimens may be investigated in the USA.

For subsequent therapy, recommendations include the following options [22, 34]. For patients with acute or lymphoma types who achieve initial response to primary therapy, continuation of previous therapy or allogeneic hematopoietic stem cell transplantation (allo-HSCT) may be appropriate. Reports have shown that autologous transplantation is of little benefit for patients with ATL [40]. A recent retrospective analysis from Japan suggests that allo-HSCT at first remission may improve OS in some patients [25]. Patient age is a key factor in determining the appropriateness of allo-HSCT and the type of conditioning regimen used (i.e., myeloablative vs reduced intensity) [25]. The mean age of onset of ATL has increased in Japan [25] and is higher compared with other regions (e.g., the Caribbean) [10, 11]; thus, patterns of allo-HSCT use may vary over time and by location. In addition, the ability to find appropriate matched donors affects the use of allo-HSCT. The role of haplo-identical allo-HSCT in this context remains to be determined [41].

Patients with acute or lymphoma types who do not respond to primary therapy are a population with a significant unmet medical need; outcomes are dismal for these patients, and evidence-based treatments are lacking. Options for treatment of R/R ATL are very limited and might include a clinical trial, best supportive care, or an alternate therapy not previously used (such as AZT/IFN for acute or chemotherapy for lymphoma) [22, 34]. Registry studies from Japan indicate that allo-HSCT has been used in patients who were not in complete remission, although outcomes were poorer for patients who were not in complete remission compared with those who were [42, 43].

EMERGING TREATMENTS IN R/R ATL

A number of new agents or combination therapies are currently being investigated for treatment of ATL. Below we review several emerging treatments that have ongoing or completed clinical trials that include patients with R/R disease, a population of significant unmet need. Agents are grouped by class and presented generally in chronological order. Information regarding clinical trials for emerging therapies in patients with R/R ATL is summarized in Table 1 [35, 44–58].

Antimetabolites

Cladribine

Cladribine is a purine nucleoside analogue resistant to degradation by adenosine deaminase [59, 60]. It is approved in the USA, European Union, and Japan for treatment of hairy cell leukemia [59, 60].

Phosphorylated derivatives of cladribine accumulate in lymphocytes with high deoxycytidine kinase activity, resulting in DNA strand breaks and cell death [44, 59, 60]. Cladribine is distinct among nucleoside analogues in that it is toxic in both rapidly proliferating cells and in resting cells [59, 60]. Cladribine was evaluated in a phase 2 trial in patients with R/R ATL (acute, lymphoma, or unfavorable chronic); however, it was terminated because of the low efficacy in futility analysis [44] (see Table 1).

Clofarabine

Clofarabine is a purine nucleoside metabolic inhibitor [61] that is structurally related to cladribine [62]. It is approved in the USA and European Union for treatment of pediatric patients 1–21 years old with R/R acute lymphoblastic leukemia after at least two prior regimens [61, 63].

Clofarabine inhibits DNA polymerases and ribonucleoside reductase; it also causes disruption of mitochondrial membrane integrity with release of cytochrome C and other apoptosis-inducing factors, leading to programmed cell death [61, 63]. A phase 1/2 study of the nucleoside analogue clofarabine in patients with R/R T-cell or natural killer (NK) cell lymphoma, including R/R ATL (NCT00416351), is ongoing.

Pralatrexate

Pralatrexate is a folate analogue metabolic inhibitor. It is currently approved in the USA for the treatment of patients with R/R PTCL [64].

Pralatrexate competitively inhibits dihydrofolate reductase and is a competitive inhibitor for polyglutamylation by the enzyme folylpolyglutamyl synthetase. This inhibition results in the depletion of thymidine and other biologic molecules [64].

The PROPEL study was a phase 2 study of pralatrexate in patients with R/R PTCL (however, the study population included only one patient with ATL) [65]. A phase 1/2a study evaluating pralatrexate plus the histone deacetylase (HDAC) inhibitor romidepsin in R/R lymphoid malignancies (including ATL) or multiple myeloma is currently recruiting (NCT01947140) (see Table 1).

Monoclonal Antibodies

Mogamulizumab

Mogamulizumab is a novel, defucosylated, humanized, monoclonal antibody targeting CCR4 [66]. CCR4 is one of the chemokine receptors involved in leukocyte migration and is selectively expressed in type 2 helper T cells (Th2) and regulatory T (T_{reg}) cells [67]. CCR4 is often shown to be expressed in certain hematologic malignancies [67]. It is currently approved in Japan for the treatment of patients with treatment-naïve or R/R CCR4+ ATL as well as for R/R CCR4+ PTCL and cutaneous T-cell lymphoma (CTCL) [68]. Mogamulizumab in combination with dose-intensified chemotherapy has also demonstrated efficacy in newly diagnosed ATL [69].

Mogamulizumab demonstrates multiple potential mechanisms of action. It demonstrates potent antitumor activity and is mediated by highly enhanced antibody-dependent cellular cytotoxicity (ADCC) [70] because of its reduced fucose content [71]. Mogamulizumab

Table 1 Emerging treatments with completed or ongoing clinical trials

Agent Trial (location)	Phase	*N*	Patients	Results/efficacy	Most common AEs (all grades, unless otherwise stated)
Antimetabolites					
Cladribine					
Tobinai [44] (Japan)	2	15	R/R ATL (acute, lymphoma, or unfavorable chronic)	ORR: 7% (1 PR)	Grade ≥ 3 Neutropenia (44%) Leukopenia (31%) Anemia (25%) All grades Neutropenia (63%) Leukopenia (56%) Anemia (31%) Thrombocytopenia (31%)
Clofarabine					
NCT00416351 (USA)	1/2	29	R/R T-cell or NK cell lymphoma, including ATL	Study is ongoing; not recruiting	
Pralatrexate					
+ Romidepsin NCT01947140 (USA)	1/2	93	R/R lymphoid malignancies and multiple myeloma (phase 1); R/R T-cell lymphoma (phase 2)	Study is recruiting	
AZT/IFN combinations					
AZT and/or IFN plus arsenic trioxide					
Hermine [45] (France)	2	7	R/R ATL (4 acute, 3 lymphoma)	ORR: 57% (4/7; 1 CR) Median OS: 1.5 months	Hematologic toxicity (86% [6/7]) Neuropsychiatric (86%) GI (57%)
Monoclonal antibodies					
Mogamulizumab					
Yamamoto [46] (Japan)	1	16	Relapsed CCR4$^+$ ATL/PTCL	ORR: 31% (5/16) CR: 13% (2/16) Median PFS: 46 days	Hematologic toxicity (88%) Infusion-related reaction (88%)
Ishida [47] (Japan)	2	26	Relapsed aggressive CCR4$^+$ ATL	ORR: 50% (13/26) CR: 31% (8/26) Median PFS: 5.2 months Median OS: 13.7 months	Hematologic toxicity (96%) Infusion-related reaction (89%) Skin rash (63%)
Phillips [48] (US/EU/LA)	2	71 (Moga: 47; IC: 24)	R/R ATL	ORR: Moga: 28% (13/47); IC: 8% (2/24) Median PFS: Moga: 0.9 months; IC: 0.9 months Median OS: Moga: 4.9 months; IC: 6.9 months	TEAEs occurring more often in the Moga group than the IC group: Infections (51% vs 21%) Respiratory disorders (49% vs 29%) Infusion-related reactions (47% vs 0%) Skin disorders (43% vs 8%) TEAEs ≥ grade 3 Moga: 62% (29/47) IC: 54% (13/24)

Table 1 continued

AgentTrial (location)	Phase	*N*	Patients	Results/efficacy	Most common AEs (all grades, unless otherwise stated)
Daclizumab					
Berkowitz [49] (USA)	2	20	ATL (all subtypes; 70% had received previous therapy)	ORR: 20% (all indolent) Median PFS: 12 weeks Median OS: 132.6 weeks	Hypoglycemia (50%) Hyperuricemia (45%) AST (40%) Hypoalbuminemia (40%) Diarrhea (25%)
Brentuximab					
NCT01703949 (USA)	Pilot	8	R/R CD30+ lymphoma (including ATL)	Study is ongoing; not recruiting	
NCT02588651 (USA)	2	31	R/R CD30-low mature T-cell lymphoma (including ATL)	Study is recruiting	
Alemtuzumab					
Sharma [50] (USA)	2	29	Acute, chronic, or lymphomatous ATL with at least 10% of malignant cells expressing CD52 and CD25 (69% had prior treatment)	ORR: 52% CR: 21% Median PFS: 2.0 months Median OS: 5.9 months	All patients developed CMV antigenemia Grade 3 and 4 AEs $\geq$ 10% Leukopenia (41% grade 3; 17% grade 4) Neutropenia (31% grade 3; 3% grade 4) Lymphocytopenia (59% grade 3) Anemia (24% grade 3) Infections (14% grade 3) Thrombocytopenia (10% grade 3) Hypotension (10% grade 3) Fever in absence of neutropenia (10% grade 3)
Proteasome inhibitor					
Bortezomib					
Ishitsuka [51] (Japan)	2	15	R/R ATL	ORR: 7% PFS: 38.0 days (study terminated because of unpromising results)	Fever (47%) Anorexia (40%) Thrombocytopenia (73%) Leukopenia (33%) Lymphopenia (33%)

Table 1 continued

Agent Trial (location)	Phase	*N*	Patients	Results/efficacy	Most common AEs (all grades, unless otherwise stated)
+ EPOCH and raltegravir Ratner [35] (USA)	1/2	18	Previously treated ($n = 4$) or untreated ($n = 14$) acute or lymphoma ATL	ORR: 61% (11/18) CR: 17% (3/18) Median PFS: 5.8 months Median OS: 6.2 months	Grade 4 toxicities Neutropenias ($n = 5$) Thrombocytopenias ($n = 4$) Leukopenias ($n = 2$) Sepsis ($n = 1$) Neutropenic fever ($n = 1$) Grade 3 toxicities Hematologic ($n = 11$) Gastrointestinal ($n = 5$) Metabolic ($n = 5$) Pulmonary ($n = 2$) Infectious ($n = 2$)
Carfilzomib					
NCT01336920 (USA)	1	15	R/R T-cell lymphoma (including ATL)	Study is ongoing, not recruiting	
Aurora A kinase inhibitor					
Alisertib					
Barr [52] (USA)	2	37 (ATL: $n = 4$)	R/R PTCL (including ATL)	ORR (ATL): 25% (1/4)	Grade ≥ 3 (all patients) Neutropenia (32%) Anemia (30%) Thrombocytopenia (24%) Any grade (all patients) Anemia (59%) Thrombocytopenia (46%) Fatigue (46%)
+ Vorinostat NCT01567709 (USA)	1	60	R/R Hodgkin lymphoma, B-cell NHL, or PTCL (including ATL)	Study is ongoing; not recruiting	
Immunomodulatory agents					
Lenalidomide					
Ishida [53] (Japan)	2	26	R/R aggressive (acute, lymphoma, or unfavorable chronic) ATL	ORR: 42% (11/26) CR/CRu: 19% (5/26) Median PFS: 3.8 months Median OS: 20.3 months	Grade 3/4 Neutropenia (65%) Leukopenia (38%) Lymphopenia (38%) Thrombocytopenia (23%) Anemia (19%)
Phillips [54] (North America)	2	4 (study closed early because of limited patient accrual)	R/R acute or lymphoma ATL	ORR: 0 OS: range: 7–62 months	Grade 1 fatigue (75%) Grade 1 thrombocytopenia (50%) No grade 3 or 4 AEs

Table 1 continued

AgentTrial (location)	Phase	*N*	Patients	Results/efficacy	Most common AEs (all grades, unless otherwise stated)
Ogura [55] (Japan)	1	13 (ATL: $n = 9$)	Advanced (previously treated; relapsed/progressed) ATL (acute, lymphoma, or unfavorable chronic)/PTCL	ORR: 36% (4/13; all PR) Median PFS: 3.4 months	Lymphopenia (11 [85%]) Neutropenia (11 [85%]) Thrombocytopenia (10 [77%]) Anemia (10 [77%]) Increased alanine aminotransferase (11 [85%]) Increased aspartate aminotransferase (11 [85%]) Maculopapular rash (9 [69%]) Increased blood alkaline phosphatase (8 [62%]) Increased C-reactive protein (8 [62%]) Hypoalbuminemia (8 [62%]) Hypophosphatemia (8 [62%])
Therapeutic vaccines					
TAX DC vaccine					
Suehiro [56] (Japan)	Pilot	3	Previously treated ATL	ORR: 2/3 (PR) Duration of remission (range): 19+–24+ months	Fever (3/3) Dermatitis (3/3) Diarrhea (1/3)
THV-02					
Trials planned [57]	N/A	N/A	N/A	N/A	N/A
Immune toxins					
IMTOX-25					
NCT01378871 (USA)	2	1	R/R CD25+ ATL	Study completed; no results available	
LMB-2					
+ Fludarabine and cyclophosphamide Kreitman [58] (USA)	2	17	Previously treated ($n = 16$) or untreated ($n = 1$) CD25+ ATL	CR: 6/15 PR: 2/15 Median PFS: 11.6 months (responders); 1.1 months (nonresponders)	Grade ≥ 3 Neutropenia ($n = 12$) Leukopenia/lymphopenia ($n = 12$) Anemia ($n = 8$) Transaminases ($n = 5$) Thrombocytopenia ($n = 6$) Fever/chills ($n = 4$)
JAK inhibitor					
Ruxolitinib					
NCT01712659 (USA)	2	20	Smoldering or chronic ATL or previously treated lymphomatous or acute ATL with clinically indolent behavior (lack of significant symptoms and treatment-free interval > 6 months)	Study is recruiting	
NCT01431209 (USA)	2	90	R/R diffuse large B-cell or peripheral T-cell NHL	Study is recruiting	

Table 1 continued

Agent Trial (location)	Phase	*N*	Patients	Results/efficacy	Most common AEs (all grades, unless otherwise stated)
Histone deacetylase inhibitor					
Panobinostat					
NCT01261247 (USA)	2	41	R/R NHL (including recurrent ATL)	Study is ongoing; not recruiting	
HBI-8000					
NCT02955589 (Japan)	2	30	R/R ATL	Study is recruiting	
Checkpoint inhibitor (PD-1 antibody)					
Pembrolizumab					
NCT02535247 (USA)	2	24 (planned)	R/R peripheral T-cell NHL (including ATL)	Study is recruiting	
PI3K inhibitor					
RP6530					
NCT02567656 (USA)	1	58 (planned)	R/R peripheral or cutaneous T-cell lymphoma	Study is recruiting	

AE adverse event, *AST* aspartate aminotransferase, *ATL* adult T-cell leukemia–lymphoma, *CCR4* C–C chemokine receptor 4, *CR* complete response, *CRu* complete response unconfirmed, *GI* gastrointestinal, *IC* investigator's choice, *JAK* Janus kinase, *NHL* non-Hodgkin lymphoma, *NK* natural killer, *ORR* overall response rate, *OS* overall survival, *PFS* progression-free survival, *PR* partial response, *PTCL* peripheral T-cell lymphoma, *R/R* relapsed/refractory, *TEAE* treatment emergent adverse event

also has been shown to deplete T_{reg} cells, resulting in increased antitumor immune response [72, 73], thereby demonstrating activity as an immune-oncology agent. A recent translational study in patients with advanced or recurrent CCR4-negative solid cancers demonstrated that mogamulizumab depleted FoxP3+ CD4 T_{reg} cells and that the effect was generally durable for more than 6 months after finishing eight infusions of mogamulizumab [74]. The depletion of T_{reg} cells may explain why mogamulizumab use in the pre-transplantation setting has been associated with an increased risk of severe graft-versus-host disease (GVHD) and GVHD-related mortality [75, 76].

Completed clinical trials of mogamulizumab in ATL include a phase 1 trial in relapsed ATL/PTCL [46] and a phase 2 trial in relapsed ATL [47]. A phase 2 study in previously treated ATL vs investigator's choice is currently ongoing [48] (see Table 1).

Daclizumab

Daclizumab is an anti-CD25 antibody [49]. It had been approved in the USA and European Union for prevention of acute allograft rejection, but manufacturing stopped in 2009. A new form (daclizumab high-yield process) is currently under review in the USA and European Union for treatment of relapsing multiple sclerosis.

Daclizumab acts by blocking CD25 (IL2R-α), thereby preventing the interaction of IL-2 with the high-affinity receptor and decreasing IL-2-mediated maintenance of the cytokine-dependent target cells [49]. A completed phase 2 trial evaluated daclizumab in patients with all subtypes of ATL (the majority of whom had received previous treatment) [49] (see Table 1).

Brentuximab Vedotin

Brentuximab vedotin is an antibody–drug conjugate (ADC). It is currently approved in the USA and European Union for treatment of patients with Hodgkin lymphoma (CD30+ HL, specifically, in the European Union) after failure of autologous stem cell transplant (ASCT) or after failure of at least two previous multi-agent chemotherapy regimens in patients who are not ASCT candidates, for patients with R/R systemic anaplastic large cell lymphoma (after failure of at least one previous multi-agent chemotherapy regimen in the USA), and in the USA for patients with primary cutaneous anaplastic

large cell lymphoma or CD30+ mycosis fungoides (MF) who have received prior systemic therapy [77, 78].

Brentuximab vedotin is an anti-CD30 monoclonal antibody attached by a protease-cleavable linker to a cytotoxic agent, the microtubule-disrupting agent monomethyl auristatin E (MMAE). Following binding of the ADC to CD30-expressing cells and internalization of the ADC–CD30 complex, MMAE is released by proteolytic cleavage, resulting in targeted cell death via the microtubule-disrupting actions of MMAE [77–79].

Clinical trials include two ongoing trials in patients with R/R CD30+ lymphomas, including some ATL patients (a pilot study in patients with R/R disease [NCT01703949] and a phase 2 study in R/R CD30-low mature T-cell lymphomas [NCT01805037]) (see Table 1).

Alemtuzumab

Alemtuzumab is a CD52-directed cytolytic antibody approved in the USA for treatment of B-cell chronic lymphocytic leukemia [80].

Alemtuzumab binds to CD52, an abundant membrane glycoprotein expressed on the surface of B and T lymphocytes, monocytes, macrophages, and eosinophils [80, 81]. This binding results in complement-mediated lysis and ADCC through activation of NK cells and macrophages [80, 81]. A completed phase 2 study evaluated alemtuzumab in patients with chronic, acute, and lymphomatous ATL, the majority of whom had received prior treatment for ATL [50] (see Table 1).

Proteasome Inhibitor

Bortezomib

Bortezomib is a proteasome inhibitor approved in the USA and by the European Medicines Agency (EMA) for treatment of patients with multiple myeloma and patients with mantle cell lymphoma [82, 83].

Bortezomib reversibly inhibits activity of the 26S proteasome (a large protein complex that degrades ubiquitinated proteins), which prevents targeted proteolysis within the cell (including blockade of the degradation of IkBα, which prevents the activation of nuclear factor-kB [NF-kB] [51]), affecting multiple signaling cascades and ultimately leading to cell death [82, 83]. Bortezomib may also increase sensitivity of cancer cells to traditional anticancer agents. Clinical trials include a phase 2 trial with bortezomib monotherapy in R/R ATL (study terminated because of unpromising results) [51]; and a recently completed phase 1/2 trial of EPOCH with bortezomib and the integrase inhibitor raltegravir in previously treated or untreated ATL [35] (see Table 1).

Aurora A Kinase Inhibitor

Alisertib

Alisertib is an investigational Aurora A kinase (AAK) inhibitor. Alisertib causes G2/M arrest, abnormal mitotic spindle formation, the appearance of tetraploidy, and subsequent apoptosis [52]. A completed phase 2 clinical trial evaluated alisertib in patients with R/R PTCL (that included four patients with R/R ATL) [52]. A phase 1 trial of alisertib plus the HDAC inhibitor vorinostat in patients with R/R Hodgkin lymphoma, B-cell NHL, or PTCL (including ATL; NCT01567709) is ongoing (see Table 1).

Immunomodulatory Agents

Lenalidomide

Lenalidomide is a thalidomide analogue that is an immunomodulatory agent with antiangiogenic and antineoplastic properties [84]. It is currently approved by the US Food and Drug Administration (FDA) and the EMA for treatment of multiple myeloma (MM), transfusion-dependent anemia due to low- or intermediate-1-risk myelodysplastic syndromes (MDS) associated with a deletion 5q abnormality with or without additional cytogenetic abnormalities [84, 85], and, in the USA, is also approved for treatment of relapsed or progressed mantle cell lymphoma (MCL) [84].

Lenalidomide inhibits proliferation and induces apoptosis of certain hematopoietic tumor cells, including multiple myeloma, mantle cell lymphoma, and del (5q) MDS, and

causes a delay in tumor growth in some hematopoietic tumor models, including multiple myeloma. Immunomodulatory properties of lenalidomide include activation of T cells and NK cells, increased numbers of NKT cells, and inhibition of pro-inflammatory cytokines (e.g., TNF-α and IL-6) by monocytes [84, 85].

Completed clinical trials with lenalidomide in patients with R/R ATL include a multicenter, open-label, phase 1 study in patients with relapsed ATL (or PTCL) [55], a multicenter, open-label, phase 2 study in Japan [53], and a phase 2 study in North America [54] (see Table 1).

Therapeutic Vaccines

Therapeutic vaccines would offer a novel mechanism for treating ATL by means of stimulating an immune response against HTLV-1. Although still early in development, these agents may provide additional options for R/R ATL.

The Tax peptide-pulsed dendritic cell (Tax-DC) vaccine was designed to augment an HTLV-I Tax-specific cytotoxic T lymphocyte (CTL) response that has been implicated in anti-ATL effects [56]. It consists of autologous DCs pulsed with Tax peptides corresponding to the CTL epitopes [56]. Clinical trials include a pilot study of three patients with ATL who were previously treated and classified as intermediate to high risk [56].

THV02 is a therapeutic vaccine candidate for treatment of ATL. THV02 comprises two lentiviral vectors to be used in a prime/boost regimen [57]. THV02 encodes for a unique polypeptide derived from Tax, HBZ, p12I and p30II proteins, involved in HTLV-1 pathogenicity and known to be recognized by the immune system of HTLV-1 infected patients [86]. Preclinical results have demonstrated that THV02 can induce a cellular immune response in animal models [86]. THV02 was granted Orphan Drug Designation in 2015 by the EMA on the basis of preclinical immunogenicity results; clinical trials in ATL are planned [57].

Others

Agents with Clinical Trial Results in Patients with R/R ATL

Arsenic trioxide has been evaluated in combination with IFN in patients with R/R ATL (results summarized in Table 1) [45] and demonstrated efficacy in combination with AZT and IFN in patients with newly diagnosed chronic ATL [87, 88]. In lymphoma, the combination of IFN/AZT/arsenic increased the time to progression (Hermine et al., unpublished data). The anti-CD25 recombinant immunotoxin LMB-2 in combination with fludarabine and cyclophosphamide was evaluated in a phase 2 study in patients with CD25+ ATL, the majority of whom were previously treated (see Table 1) [58].

Agents with Completed (But Unpublished) or Ongoing Studies in R/R ATL

A phase 1 study of the proteasome inhibitor carfilzomib in patients with R/R T-cell lymphoma, including R/R ATL (NCT01336920) is ongoing (not recruiting). A phase 2 study of the immune toxin IMTOX-25 in patients with R/R CD25+ ATL (NCT01378871) has been completed; results have not yet been published. Two studies of the JAK inhibitor ruxolitinib are currently recruiting: a phase 2 study in patients with smoldering or chronic ATL [or previously treated lymphomatous or acute ATL with clinically indolent behavior indicated by lack of significant symptoms and treatment-free interval of greater than 6 months (NCT01712659)] and a phase 2 study in patients with R/R diffuse large B-cell or peripheral T-cell NHL, including ATL (NCT01431209). Studies of HDAC inhibitors include a phase 2 study of panobinostat in patients with R/R NHL (including recurrent ATL) that is currently ongoing (NCT01261247) and a phase 2 study of HBI-8000 in patients with R/R ATL that is currently recruiting (NCT02955589). A study of the PD-1 antibody pembrolizumab in R/R peripheral T-cell NHL (including ATL) is currently recruiting (NCT02535247). A phase 1 study of the dual PI3 K delta/gamma inhibitor RP6530 in patients with R/R peripheral (or cutaneous) T-cell

lymphomas is currently recruiting (NCT02567656). See Table 1 for additional information on these studies.

Selected Agents with Studies in ATL and Related Conditions

Additional studies of HDAC inhibitors and checkpoint inhibitors in patients with ATL (not specifically R/R ATL) and other T-cell malignancies are also of interest. The HDAC inhibitors romidepsin and vorinostat have demonstrated efficacy in and are FDA approved for treatment of R/R cutaneous T-cell lymphoma [89–92]. Studies of HDAC inhibitors (in combination with AZT and/or IFN) in patients with ATL include a recently completed phase 1/2 trial that evaluated valproic acid in combination with AZT/IFN as maintenance therapy (NCT00854581) [93] and an ongoing study of belinostat in combination with AZT as consolidation therapy (NCT02737046) [94]. Clinical trials of checkpoint inhibitors include a phase 2 study of the PD-1 antibody nivolumab in patients with ATL (NCT02631746).

CONCLUSIONS

Patients with ATL are rarely cured with currently available cytotoxic drugs. Only those with chronic forms treated with antiviral therapy experienced long survival. In aggressive forms, only allo-HSCT after cytotoxic chemotherapy can cure some patients. The use of higher dose of chemotherapies and/or new cytotoxic agents did not significantly improve overall survival. At the present time, it is not yet clear whether increased response rates seen with combinations of monoclonal antibodies and chemotherapies could translate into an improvement of overall survival. Patients with R/R disease face a difficult prognosis and a limited number of treatment options. A number of different treatments have been and are being studied for use in R/R ATL, including several that are commercially available and approved for other indications. Emerging therapies with novel mechanisms of action and that target different pathways may further expand the number of available treatment options and improve outcomes for patients with R/R ATL. Therapies which aim to increase immune response may be of particular interest in this disease.

ACKNOWLEDGEMENTS

Funding. Funding to support the preparation of this manuscript, article processing charges, and open access fee was provided by Kyowa Kirin International (Bedminster, NJ, USA), a subsidiary of Kyowa Hakko Kirin Co. Ltd.

Medical Writing, Editorial, and Other Assistance. The authors thank Sherri D. Jones of MedVal Scientific Information Services, LLC for medical writing and editorial assistance, for which funding was provided to MedVal by Kyowa Kirin International, a subsidiary of Kyowa Hakko Kirin Co. Ltd. This manuscript was prepared according to the International Society for Medical Publication Professionals' "Good Publication Practice for Communicating Company-Sponsored Medical Research: The GPP3 Guidelines."

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval for the version to be published. All authors contributed equally and each were involved in data analysis/interpretation and in drafting or critically revising the manuscript.

Disclosures. Olivier Hermine has nothing to declare. Juan Carlos Ramos has nothing to declare. Kensei Tobinai received research funding from Kyowa Hakko Kirin, Celgene, Eisai, Mundipharma, Takeda; and has received honoraria from Eisai, Takeda, Mundipharma, HUYA Bioscience International, Kyowa Hakko Kirin, Celgene.

Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

Data Availability. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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