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SPECIAL ARTICLE

Definition, Prognostic Factors, Treatment, and Response Criteria of Adult T-Cell Leukemia-Lymphoma: A Proposal From an International Consensus Meeting

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ABSTRACT

Adult T-cell leukemia-lymphoma (ATL) is a distinct peripheral T-lymphocytic malignancy associated with a retrovirus designated human T-cell lymphotropic virus type I (HTLV-1). The diversity in clinical features and prognosis of patients with this disease has led to its subclassification into the following four categories: acute, lymphoma, chronic, and smoldering types. The chronic and smoldering subtypes are considered indolent and are usually managed with watchful waiting until disease progression, analogous to the management of some patients with chronic lymphoid leukemia (CLL) or other indolent histology lymphomas. Patients with aggressive ATL generally have a poor prognosis because of multidrug resistance of malignant cells, a large tumor burden with multiorgan failure, hypercalcemia, and/or frequent infectious complications as a result of a profound T-cell immunodeficiency. Under the sponsorship of the 13th International Conference on Human Retrovirology: HTLV, a group of ATL researchers joined to form a consensus statement based on established data to define prognostic factors, clinical subclassifications, and treatment strategies. A set of response criteria specific for ATL reflecting a combination of those for lymphoma and CLL was proposed. Clinical subclassification is useful but is limited because of the diverse prognosis among each subtype. Molecular abnormalities within the host genome, such as tumor suppressor genes, may account for these diversities. A treatment strategy based on the clinical subclassification and prognostic factors is suggested, including watchful waiting approach, chemotherapy, antiviral therapy, allogeneic hematopoietic stem-cell transplantation (alloHSCT), and targeted therapies.

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DEFINITION

Adult T-cell leukemia-lymphoma (ATL) is a distinct peripheral T-lymphocytic malignancy associated with a retrovirus designated human T-cell leukemia virus type 1 or human T-cell lymphotropic virus type 1 (HTLV-1).[1-3] We recommend following the WHO classification of ATL published in 2001.[4]

PROGNOSTIC FACTORS

Major prognostic indicators[5-8] for ATL have been elucidated in 854 patients; advanced performance status (PS), high lactic dehydrogenase (LDH) level, age ≥ 40 years, more than three involved lesions, and hypercalcemia[5] are prognostic factors that have been identified by multivariate analysis. These factors were used to construct a risk model.[5] Additional factors associated with poor prognosis include thrombocytopenia,[9] eosinophilia,[10] bone marrow involvement,[11] high interleukin-5 serum level,[12] C-C chemokine receptor 4 expression,[13] lung resistance–related protein,[14] *p53* mutation,[15] and *p16* deletion.[9] For the chronic type of ATL, high LDH, high blood urea nitrogen, and low albumin levels have been identified as poor prognostic factors by multivariate analysis.[6] Univariate analysis has revealed that neutrophilia,[11] *p16* deletion,[9] and chromosomal deletion detected by comparative genomic hybridization[16] are associated with poor prognosis in chronic ATL. In contrast, chronic lymphoid leukemia (CLL)–like morphology of ATL cells was associated with longer transformation-free survival of chronic ATL.[17] Primary cutaneous tumoral type, although generally included among smoldering ATL, was a poor prognostic factor by univariate analyses.[18] A combination of these and more novel prognostic factors may be superior to elucidate better risk ATL groups for stratification of treatment decision than the Shimoyama criteria, which stratify

ATL into four clinical subtypes or risk groups, although these factors have not been evaluated simultaneously by a multivariate analysis.[5,19] Of note, these prognostic factors may not have to be applied when considering new therapeutic strategies (eg, antiretroviral therapies).

There are limited data comparing Japanese patients with those in the other countries, and there are no prospective studies addressing this issue.[18,20-22] In a retrospective review of 89 patients predominantly of Caribbean origin, the median age at diagnosis was 50 years, whereas in the Japanese population, it is 57 years.[20] In addition, survival times according to the Shimoyama subclassification in both Caribbean and Japanese populations seem to be comparable (acute: 4 *v* 6 months; lymphomatous: 9 *v* 10 months; chronic: 17 *v* 24 months; and smoldering: 34 months *v* > 5 years, respectively). Although patients of Caribbean origin with less aggressive subtypes fared worse, it is not clear that this is statistically significant.

CLINICAL SUBCLASSIFICATION

Criteria

We recommend following the Shimoyama criteria on ATL clinical subtype classification published in 1991.[19]

Required Evaluation

Involved organ examination: peripheral blood. The diagnosis of ATL requires detection of ATL cells in peripheral blood in patients with acute, chronic, or smoldering type with leukemic manifestations.[4,19] Typical ATL cells have markedly polylobated nuclei with homogeneous and condensed chromatin, small or absent nucleoli, and agranular and basophilic cytoplasm. These so-called flower cells are considered pathognomonic. However, the diversity of recognized ATL cell morphology is considerable.[17,23] Even in patients with extremely unusual morphology, a small percentage of prototype ATL cells have always been seen in blood films, leading to a suspected diagnosis of ATL. This should be confirmed by mature T-cell phenotype, HTLV-1 serology, and monoclonal HTLV-1 provirus in all patients.[17] Five percent or more of abnormal T lymphocytes in peripheral blood confirmed by cytology and immunophenotyping are required to diagnose ATL in patients without histologically proven tumor lesions.[19]

Bone marrow examination. A bone marrow aspiration or biopsy is generally not required to make the diagnosis of ATL. Nevertheless, assessment of the bone marrow may add useful information regarding the normal bone marrow elements before therapy. Furthermore, bone marrow involvement is an independent poor prognostic factor for ATL, similar to that found in peripheral T-cell lymphoma unspecified.[11,24]

Radiologic imaging and endoscopy. Computed tomography (CT) scans of the neck, thorax, abdomen, and pelvis are mandatory to detect sites of nodal and extranodal ATL disease. Upper GI tract endoscopy, with biopsy, should be considered because GI tract involvement is frequent in aggressive ATL.[25] These imaging modalities may detect complicated opportunistic infections including pneumonia, abscess formation, and intestinal infections such as strongyloidiasis and cytomegalovirus.[19] CNS evaluation by radiologic imaging and/or lumbar puncture for cerebral/meningeal ATL involvement or opportunistic infections should be considered for patients in the setting of altered consciousness without hypercalcemia.[26]

Biopsy. When the diagnosis of ATL is not obtained by peripheral-blood examination or when a new lesion appears during watchful waiting for indolent ATL, biopsy of suspicious lesion should be performed. Frequently involved tissues include lymph nodes, skin, liver, spleen, lung, GI tract, bone marrow, bone, and CNS.[4-8,11,25,26] As in other types of lymphomas, an excisional biopsy is recommended, instead of core needle biopsy, for lymph nodes. Whenever possible, sufficient sample should be obtained both for histopathologic examination and molecular analyses, including Southern blotting or other (eg, linker-mediated polymerase chain reaction) analysis of HTLV-1 provirus integration.

Tumor marker. Similar to serum LDH reflecting disease bulk/activity, the soluble form of interleukin-2 receptor α-chain is elevated in aggressive ATL patients, indolent ATL patients, and HTLV-1 carriers compared with normal individuals, perhaps with better accuracy than LDH.[27] These serum markers are useful to detect acute transformation of indolent ATL as well as to detect early relapse of ATL after therapy. Serum thymidine kinase levels have also been reported as a promising tumor marker for ATL.[28] However, in the current general practice for the management of ATL patients, only LDH level is required.

Immunophenotype. In most patients, ATL cells exhibit the phenotype of mature $CD4^+$ T cells and express CD2, CD5, CD25, CD45RO, CD29, T-cell receptor $\alpha\beta$, and HLA-DR.[4] Most ATL cells lack CD7 and CD26 and exhibit diminished CD3 expression. Most ATL cells are CD52 positive, but occasionally, patients are negative, and this may correlate with coexpression of CD30. Immunophenotypic analysis of CD3, CD4, CD7, CD8, and CD25 is the minimum requirement for an ATL diagnosis.

Cytogenetics. Karyotypic abnormalities revealed by conventional cytogenetics or comparative genomic hybridization are more common and complex in the acute and lymphoma types compared with the chronic type, with aneuploidy and several hot spots such as 14q and 3p.[16,29] More sensitive array-comparative genomic hybridization revealed that the lymphoma type had significantly more frequent gains at 1q, 2p, 4q, 7p, and 7q and more losses of 10p, 13q, 16q, and 18p, whereas the acute type showed a gain of 3/3p.[30] Currently, outside of clinical trials, cytogenetic analysis is not required.

Molecular biology of HTLV-1. Monoclonal integration of HTLV-1 proviral DNA is found in all cases of ATL as described in the WHO classification.[4] Integration of defective HTLV-1 into ATL cells is observed in approximately one third of ATL patients and is associated with clinical subtypes and prognosis.[31] It is recommended to perform molecular analysis of HTLV-1 integration when possible. Either Southern blotting or polymerase chain reaction for HTLV-1 can be used to identify the presence of viral integration, whereas the latter can be used for quantitative purposes. Seronegativity for HTLV-1 is quite useful to differentiate T-cell lymphomas from ATL, although HTLV-1 is not detected in lymphoma cells other than ATL. Clinically, the diagnosis of ATL is made based on seropositivity for HTLV-1 and histologically and/or cytologically proven peripheral T-cell malignancy, although rare cases of T-cell lymphomas other than ATL developing in HTLV-1 carriers have been observed.[6,8]

Molecular biology of host genome. Mutation or deletion of tumor suppressor genes, such as *p53* or $p15^{INK4B}/p16^{INK4A}$, is observed in approximately half of ATL patients and is associated with clinical subtypes and prognosis.[9,15] These new molecular markers may

help guide therapeutic decisions between conventional chemotherapy, combination of zidovudine (AZT) and interferon alfa (IFN-α), and alloHSCT. In addition to *p53* mutations when considering AZT and IFN-α combination, IRF-4 may be predictive of response.[32]

TREATMENT

Criteria for Treatment Decisions

Treatment decisions should be based on the ATL subclassification and the prognostic factors at onset and response to initial therapy (Table 1). The prognostic factors include clinical factors, such as PS, LDH, age, number of involved lesions, and hypercalcemia, and molecular factors, such as Ki-67 expression, alteration of *p53* or $p15^{INK4B}$/$p16^{INK4A}$, and overexpression of IRF-4.[5,6,8,9,15,19,33-35]

Current Treatment Options

Chemotherapy. The results of a phase III study suggest that, at the expense of higher toxicities, the vincristine, cyclophosphamide, doxorubicin, and prednisone (VCAP); doxorubicin, ranimustine, and prednisone (AMP); and vindesine, etoposide, carboplatin, and prednisone (VECP) regimen is superior to biweekly cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) in newly diagnosed acute, lymphoma, or unfavorable chronic types of ATL.[36] The rate of complete response (CR) was higher in the VCAP-AMP-VECP arm than the biweekly CHOP arm (40% *v* 25%, respectively; $P = .020$). Overall survival (OS) at 3 years was 24% in the VCAP-AMP-VECP arm and 13% in the CHOP arm ($P = .085$). However, the median survival time of 13 months still compares unfavorably to other hematologic malignancies. The superiority of VCAP-AMP-VECP to biweekly CHOP may be explained by the more prolonged, dose-dense schedule of therapy in addition to four more drugs. In addition, agents such as carboplatin and ranimustine that are not affected by multidrug resistance–related genes, which are frequently expressed in ATL cells at onset, were incorporated.[14,36] Intrathecal prophylaxis, which was incorporated in both arms of the phase III study, should be considered for patients with aggressive ATL even in the absence of clinical symptoms because a previous analysis revealed that more than half of relapses at a new site after chemotherapy occurred in the CNS.[37]

IFN-α and AZT. Numerous small phase II studies using AZT and IFN-α have shown responses in ATL patients.[38-42] High-doses of both agents are recommended (6 to 9 million units of IFN-α in combination with daily divided AZT doses of 800 to 1,000 mg/d). However, only patients with wild-type *p53* and low IFN regulatory factor 4 expression seem to exhibit long-term responses to AZT/IFN-α therapy.[32,43,44]

The results of a recent worldwide meta-analysis on the use of AZT/IFN for ATL in 209 patients treated from 1994 to 2006 were presented at the 13th International Conference on Human Retrovirology: HTLV and at the 49th Annual Meeting of the American Society of Hematology.[21,22] One hundred patients received first-line AZT/IFN-α therapy. In these patients, the response rate was 66%, including 43% of patients achieving CR. In patients treated with first-line AZT/IFN-α, the median survival time was 24 months, and the 5-year OS rate was 50%, whereas these values were 7 months and 20%, respectively, in 84 patients who received first-line chemotherapy. The

Table 1. Recommended Strategy for the Treatment of ATL

Smoldering- or favorable chronic-type ATL
Consider inclusion in prospective clinical trials
Symptomatic patients (skin lesions, opportunistic infections, and so on): consider AZT/IFN-α or watch and wait
Asymptomatic patients: consider watch and wait
Unfavorable chronic- or acute-type ATL
Recommend: inclusion in prospective clinical trials
If outside clinical trials, check prognostic factors (including clinical and molecular factors if possible):
Good prognostic factors: consider chemotherapy (VCAP-AMP-VECP evaluated by a randomized phase III trial against biweekly CHOP) or AZT/IFN-α (evaluated by a retrospective worldwide meta-analysis)
Poor prognostic factors: consider chemotherapy followed by conventional or reduced-intensity allogeneic HSCT (evaluated by retrospective or prospective Japanese analyses, respectively)
Poor response to initial therapy with chemotherapy or AZT/IFN-α: consider conventional or reduced-intensity allogeneic HSCT
Lymphoma-type ATL
Recommend: inclusion in prospective clinical trials
If outside clinical trials, consider chemotherapy (VCAP-AMP-VECP)
Check prognostic factors and response to chemotherapy (including clinical and molecular factors if possible):
Favorable prognostic profiles and good response to initial therapy: consider chemotherapy
Unfavorable prognostic profiles or poor response to initial therapy with chemotherapy: consider conventional or reduced-intensity allogeneic HSCT
Options for clinical trials (first line)
Test the effect of up-front allogeneic HSCT
Test promising targeted therapies such as arsenic trioxide + IFN-α, bortezomib + chemotherapy, or antiangiogenic therapy
Consider a phase II global study testing pegylated IFN and AZT
Options for clinical trials (relapse or progressive disease)
Test the effect of promising targeted therapies such as arsenic trioxide and IFN-α, bortezomib, a purine nucleotide phosphorylase inhibitor, histone deacetylase inhibitors, monoclonal antibodies, antiangiogenic therapy, and survivin, β-catenin, syk, and lyn inhibitors, etc.
Consider conventional or reduced-intensity allogeneic HSCT when possible

Abbreviations: ATL, adult T-cell leukemia-lymphoma; AZT, zidovudine; IFN-α, interferon alfa; VCAP-AMP-VECP, vincristine, cyclophosphamide, doxorubicin, and prednisone; doxorubicin, ranimustine, and prednisone; and vindesine, etoposide, carboplatin, and prednisone; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; HSCT, hematopoietic stem-cell transplantation.

median survival times of patients with acute-type ATL treated with first-line AZT/IFN-α and chemotherapy were 12 and 9 months, respectively. However, achievement of CR with first-line AZT/IFN-α therapy resulted in a prolonged survival time of more than 10 years in 70% of the study population and 75% of the acute-type ATL subgroup. Patients with lymphoma-type ATL did not benefit from AZT/IFN-α therapy; the median survival times of these patients treated with first-line AZT/IFN-α and chemotherapy were 12 and 15 months, respectively. Finally, first-line AZT/IFN-α therapy in chronic- and smoldering-type ATL resulted in 100% OS at a median follow-up time of 5 years. Although the results for AZT/IFN-α in indolent ATL seem to be promising compared with the results seen with watchful waiting until disease progression recently reported from Japan,[45] the possibility of selection bias cannot be ruled out. In conclusion, these results suggest that treatment of ATL using AZT/IFN-α results in high response and CR rates particularly in acute, chronic, and smoldering types of ATL, resulting in prolonged survival in a significant proportion of patients. Although this is a retrospective analysis, the results seem to be promising, and further studies comparing AZT/IFN-α and chemotherapy in acute ATL are warranted.

alloHSCT. alloHSCT is now considered a promising treatment of young patients with aggressive ATL. Despite higher treatment-related mortality in a retrospective multicenter analysis, the estimated 3-year OS rate of 45% is promising, possibly reflecting a graft-versus-ATL effect.[46] A phase I trial of alloHSCT with reduced-intensity conditioning for ATL also revealed promising results. Minimal residual disease after alloHSCT detected by proviral load was much less compared with that after chemotherapy or AZT/IFN-α therapy, suggesting the presence of a graft-versus-ATL effect as well as graft-versus-HTLV-1 activity.[47] It remains uncertain which type of alloHSCT (myeloablative or reduced-intensity conditioning) is most suitable for the treatment of ATL. However, myeloablative alloHSCT, but not reduced-intensity conditioning alloHSCT, might be considered for the treatment of patients with progressive disease (PD) at relapse as well as at onset. Furthermore, selection criteria with respect to response to previous treatments, sources of stem cells, and HTLV-1 viral status of the donor remain to be determined.

Required Pretreatment Evaluation

The diagnosis of ATL is based on HTLV-1 seropositivity and histologically and/or cytologically proven peripheral T-cell malignancy as described in the WHO classification.[4] In uncertain cases, Southern blot hybridization for monoclonal integration of HTLV-1 provirus is useful for the diagnosis, although the sensitivity is to detect the presence of approximately 5% or more monoclonal ATL cells in peripheral-blood mononuclear cells or fresh biopsy.[6]

Traditionally, patients with indolent ATL (ie, the chronic or smoldering type) have been managed similarly to patients with CLL, with a watchful waiting policy until disease progression.[6,8,9] In the consecutive trials for aggressive ATL by Japan Clinical Oncology Group (JCOG)–Lymphoma Study Group, previously untreated patients with aggressive ATL (ie, acute-, lymphoma-, or unfavorable chronic-type ATL) were eligible for participation.[36] Unfavorable chronic-type ATL was defined by at least one of the following three factors: a low serum albumin, high LDH, or high blood urea nitrogen concentration. Unfavorable chronic-type ATL had an unfavorable prognosis similar to acute- or lymphoma-type ATL when treated with chemotherapy.[6] In those trials, other eligibility criteria included no prior chemotherapy, age of 15 to 69 years, and Eastern Cooperative Oncology Group PS of 0 to 3 or 4 as a result of hypercalcemia.[6,36] Eligibility criteria for organ function were also described.[6,36]

Supportive Care

Sulfamethoxazole-trimethoprim and antifungal agents were recommended for the prophylaxis of *Pneumocystis jiroveci* pneumonia and fungal infections, respectively, in the JCOG trials.[6,36] Although cytomegalovirus infection commonly occurs in ATL patients, ganciclovir is not routinely recommended for prophylaxis. In addition, in patients not receiving chemotherapy, antifungal prophylaxis may not be critical. Prophylaxis with anti-*Strongyloides* agents, such as ivermectin or albendazole, should be considered to avoid systemic infection in patients with a history of past and/or present exposure to the parasite in the tropics. Treatment with corticosteroids and proton pump inhibitors may precipitate fulminant *Strongyloides* infestation and warrants testing before these agents are used in endemic areas. It is suggested that *Strongyloides* infection may increase the risk of subsequent development of ATL. Therefore, in HTLV-1 carriers, although not yet demonstrated, prophylaxis of *Strongyloides* may reduce the risk of ATL development.[48-50] Hypercalcemia associated with aggressive ATL should be managed with treatment of the disease, hydration, and bisphosphonate therapy.[6,8]

RESPONSE CRITERIA

The complex presentation of ATL, often with both leukemic and lymphomatous components, makes response assessment difficult; however, response criteria are mandatory to ensure uniform interpretation of clinical trials (Table 2). Most current ATL trials use response criteria proposed by JCOG that have been applied since 1991.[6,36] At the international consensus meetings, a modification of the JCOG criteria was suggested, reflecting the criteria for CLL and NHL that had been published later (Table 2).[51,52] CR was defined as disappearance of all clinical, microscopic, and radiographic evidence of disease. Specific lymph node requirements include that all nodes must have regressed to normal size ($\leq$ 1.5 cm in their greatest transverse diameter) and previously involved nodes that were 1.1 to 1.5 cm must have decreased to $\leq$ 1.0 cm.[51] Because HTLV-1 carriers frequently have a small percentage of abnormal lymphocytes with polylobated nuclei, so-called flower cells, in peripheral blood, provided that less than 5% of such cells remained, CR was judged to have been attained if the absolute lymphocyte count, including flower cells, was less than 4×10^9/L.[36,52] A designation of unconfirmed CR was adopted to include patients with a $\geq$ 75% reduction in tumor size but with a residual mass after treatment, as previously reported for NHL.[47] These patients must also have an absolute lymphocyte count, including flower cells, of less than 4×10^9/L. Partial response (PR) was defined as a $\geq$ 50% reduction in the sum of the products of the greatest diameters of measurable disease without the appearance of new lesions. In addition, PR was required to satisfy a 50% or greater reduction in absolute abnormal lymphocyte counts in peripheral blood. PD in peripheral blood was defined by a $\geq$ 50% increase from nadir in the count of flower cells and an absolute lymphocyte count, including flower cells, of $\geq 4 \times 10^9$/L. PD or relapsed disease in the other lesions was defined as a $\geq$ 50% increase from nadir in the sum of the products of measurable disease or the appearance of new lesions excluding skin. Stable disease

Table 2. Response Criteria for Adult T-Cell Leukemia-Lymphoma

Response	Definition	Lymph Nodes	Extranodal Masses	Spleen, Liver	Skin	Peripheral Blood	Bone Marrow
Complete remission*	Disappearance of all disease	Normal	Normal	Normal	Normal	Normal†	Normal
Uncertified complete remission*	Stable residual mass in bulky lesion	≥ 75% decrease‡	≥ 75% decrease‡	Normal	Normal	Normal†	Normal
Partial remission*	Regression of disease	≥ 50% decrease‡	≥ 50% decrease‡	No increase	≥ 50% decrease	≥ 50% decrease	Irrelevant
Stable disease*	Failure to attain complete/partial remission and no progressive disease	No change in size	No change in size	No change in size	No change in size	No change	No change
Relapsed disease or progressive disease	New or increased lesions	New or ≥ 50% increase§	New or ≥ 50% increase§	New or ≥ 50% increase	≥ 50% increase	New or ≥ 50% increase‖	Reappearance
Not assessable							

*Require each criterion to be present for a period of at least 4 weeks.
†Provided that < 5% of flower cells remained, complete remission was judged to have been attained if the absolute lymphocyte count, including flower cells, was $< 4 \times 10^9$/L.
‡Calculated by the sum of the products of the greatest diameters of measurable disease.
§Defined by ≥ 50% increase from nadir in the sum of the products of measurable disease.
‖Defined by ≥ 50% increase from nadir in the count of flower cells and an absolute lymphocyte count, including flower cells, of $> 4 \times 10^9$/L.

was defined as failure to attain CR/PR or PD. CR, unconfirmed CR, PR, and stable disease require each criterion for a period of at least 4 weeks.

Recently, revised response criteria were proposed for lymphoma. New guidelines were presented incorporating positron emission tomography (PET), especially for assessment of CR.[53] It is well known and described in the criteria that several kinds of lymphoma, including peripheral T-cell lymphomas, are variably [^{18}F]fluorodeoxyglucose avid.[53] No report described the PET results in response assessment of ATL until now. The usefulness of PET or PET/CT should be evaluated in response assessment of ATL in a prospective study. Meanwhile, PET or PET/CT should be used for evaluation of response when the tumorous lesions are fluorodeoxyglucose avid at diagnosis.

ISSUES FOR FUTURE INVESTIGATIONS IN ATL

Targeted Therapy

Several new agents against ATL are now under investigation. A promising targeted therapy for ATL is the combination of arsenic trioxide and IFN-α, which targets both Tax and the nuclear factor-κB pathway.[54-56] This combination exhibits clinical efficacy in relapsed/refractory ATL patients[57] and is currently being evaluated in untreated patients. Monoclonal antibodies against several molecules expressed on the surface of ATL cells and other lymphoid malignant cells, such as CD25, CD2, CD52, and chemokine receptor 4, have been promising in recent clinical trials. Histone deacetylase inhibitors such as vorinostat (suberoylanilide hydroxamic acid), romidepsin, and panobinostat (LBH589) have also been promising in preclinical and/or clinical studies against T-cell malignancies including ATL. Pralatrexate, a novel antifolate, and forodesine, a purine nucleotide phosphorylase inhibitor, are potential new agents with potent preclinical activity in T-cell malignancies including ATL. Other potential therapies for ATL under investigation include the combination of the proteasome inhibitor bortezomib with high-dose CHOP chemotherapy[58] and antiangiogenic therapy, such as anti–vascular endothelial growth factor monoclonal antibodies[59] or antitransferrin receptor.[60] Microarray analysis has identified survivin, β-catenin, syk, and lyn as potential targets for therapy.[61]

Prevention

Two steps should be considered for the prevention of HTLV-1–associated ATL. The first step is the prevention of HTLV-1 infection. This has been established in some HTLV-1 endemic areas in Japan by screening for HTLV-1 among blood donors and refraining from breast feeding among pregnant women who are carriers. The second step is the prevention of ATL development among HTLV-1 carriers. This has not been established partly because only approximately 5% of HTLV-1 carriers develop the disease in their lifetime and the risk factors remain unknown. Therefore, a cohort study of HTLV-1 carriers (Joint Study of Predisposing Factors for ATL Development) is ongoing nationwide in Japan.

Clinical Trials

Clinical trials have been paramount to the recent advances in ATL treatment, including assessment of chemotherapy, AZT/IFN-α, and alloHSCT, as described earlier. We have proposed a strategy for ATL treatment stratified by subclassification and prognostic factors. However, future clinical trials should be incorporated to ensure that the consensus is continually updated to establish evidence-based practice guidelines.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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