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.

AUTHOR CONTRIBUTIONS

Conception and design: Kunihiro Tsukasaki, Olivier Hermine, Ali Bazarbachi, Juan Carlos Ramos, Deirdre O'Mahony, Achiléa L. Bittencourt, Kensei Tobinai
Administrative support: Olivier Hermine, Lee Ratner, William Harrington Jr, John E. Janik, Graham P. Taylor, Kazunari Yamaguchi, Toshiki Watanabe
Collection and assembly of data: Kunihiro Tsukasaki, Olivier Hermine, Ali Bazarbachi, Juan Carlos Ramos, Deirdre O'Mahony, Achiléa L. Bittencourt, Atae Utsunomiya, Kensei Tobinai
Data analysis and interpretation: Kunihiro Tsukasaki, Olivier Hermine, Ali Bazarbachi, Lee Ratner, Juan Carlos Ramos, Deirdre O'Mahony, John E. Janik, Achiléa L. Bittencourt, Kazunari Yamaguchi, Atae Utsunomiya, Kensei Tobinai, Toshiki Watanabe
Manuscript writing: Kunihiro Tsukasaki, Olivier Hermine, Ali Bazarbachi, Lee Ratner, Juan Carlos Ramos, William Harrington Jr, Deirdre O'Mahony, John E. Janik, Achiléa L. Bittencourt, Graham P. Taylor, Kazunari Yamaguchi, Atae Utsunomiya, Kensei Tobinai, Toshiki Watanabe
Final approval of manuscript: Kunihiro Tsukasaki, Olivier Hermine, Ali Bazarbachi, Lee Ratner, Juan Carlos Ramos, William Harrington Jr, Deirdre OMahony, John E. Janik, Achiléa L. Bittencourt, Graham P. Taylor, Kazunari Yamaguchi, Atae Utsunomiya, Kensei Tobinai, Toshiki Watanabe

REFERENCES

1. Uchiyama T, Yodoi J, Sagawa K, et al: Adult T-cell leukemia: Clinical and hematologic features of 16 cases. Blood 50:481-492, 1977
2. Poiesz BJ, Ruscetti FW, Gazdar AF, et al: Detection and isolation of type C retrovirus particles from fresh and cultured lymphocytes of a patient with cutaneous T-cell lymphoma. Proc Natl Acad Sci U S A 77:7415-7419, 1980
3. Yoshida M, Miyoshi I, Hinuma Y: Isolation and characterization of retrovirus from cell lines of human adult T-cell leukemia and its implication in the disease. Proc Natl Acad Sci U S A 79:2031-2035, 1982
4. Kikuchi M, Jaffe ES, Ralfkiaer E: Adult T-cell leukaemia/lymphoma, in Jaffe ES, Harris NL, Stein H, et al (eds): WHO Classification of Tumours: Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues. Lyon, France, IARC Press, 2001, pp 200-203
5. Major prognostic factors of patients with adult T-cell leukemia-lymphoma: A cooperative study—Lymphoma Study Group (1984-1987). Leuk Res 15:81-90, 1991
6. Takatsuki K: Adult T-Cell Leukemia. New York, NY, Oxford University Press, 1994
7. International Agency for Research on Cancer Working Group on the Evaluation of Carcinogenic Risks to Humans: Human immunodeficiency viruses and human T-cell lymphotropic viruses. International Agency for Research on Cancer Monographs on the Evaluation of Carcinogenic Risks to Humans. http://monographs.iarc.fr/ENG/Monographs/vol67/volume67.pdf
8. Tobinai K, Watanabe T: Adult T-cell leukemia-lymphoma, in Abeloff MD, Armitage JO, Niederhuber JE, et al (eds): Clinical Oncology (ed 3). Philadelphia, PA, Elsevier Churchill Livingstone, 2004, pp 3109-3130
9. Yamada Y, Hatta Y, Murata K, et al: Deletions of p15 and/or p16 genes as a poor-prognosis factor in adult T-cell leukemia. J Clin Oncol 15:1778-1785, 1997
10. Utsunomiya A, Ishida T, Inagaki A, et al: Clinical significance of a blood eosinophilia in adult T-cell leukemia/lymphoma: A blood eosinophilia is a significant unfavorable prognostic factor. Leuk Res 31:915-920, 2007
11. Takasaki Y, Iwanaga M, Tsukasaki K, et al: Impact of visceral involvements and blood cell count abnormalities on survival in adult T-cell leukemia/lymphoma (ATLL). Leuk Res 31:751-757, 2007
12. Inagaki A, Ishida T, Ishii T, et al: Clinical significance of serum Th1-, Th2- and regulatory T cells-associated cytokines in adult T-cell leukemia/lymphoma: High interleukin-5 and -10 levels are significant unfavorable prognostic factors. Int J Cancer 118:3054-3061, 2006
13. Ishida T, Utsunomiya A, Iida S, et al: Clinical significance of CCR4 expression in adult T-cell leukemia/lymphoma: Its close association with skin involvement and unfavorable outcome. Clin Cancer Res 9:3625-3634, 2003
14. Ohno N, Tani A, Uozumi K, et al: Expression of functional lung resistance–related protein predicts poor outcome in adult T-cell leukemia. Blood 98: 1160-1165, 2001
15. Tawara M, Hogerzeil SJ, Yamada Y, et al: Impact of p53 aberration on the progression of adult T-cell leukemia/lymphoma. Cancer Lett 234:249-255, 2006
16. Tsukasaki K, Krebs J, Nagai K, et al: Comparative genomic hybridization analysis in adult T-cell leukemia/lymphoma: Correlation with clinical course. Blood 97:3875-3881, 2001
17. Tsukasaki K, Imaizumi Y, Tawara M, et al: Diversity of leukaemic cell morphology in ATL correlates with prognostic factors, aberrant immunophenotype and defective HTLV-1 genotype. Br J Haematol 105:369-375, 1999
18. Bittencourt AL, da Graças Vieira M, Brites CR, et al: Adult T-cell leukemia/lymphoma in Bahia, Brazil: Analysis of prognostic factors in a group of 70 patients. Am J Clin Pathol 128:875-882, 2007
19. Shimoyama M: Diagnostic criteria and classification of clinical subtypes of adult T-cell leukaemia-lymphoma: A report from the Lymphoma Study Group (1984-87). Br J Haematol 79:428-437, 1991
20. Phillips AA, Shapira I, Willim RD, et al: A multicenter clinicopathologic experience of HTLV-1 ATLL: A retrospective 15 year review reveals little progress. Blood 110:1044a, 2007 (abstr 3569)
21. Hermine O, Panelatti G, Ramos JC, et al: A worldwide meta-analysis on the use of zidovudine and interferon-alpha for the treatment of adult T-cell leukemia/lymphoma: 13th International Conference on Human Retrovirology, Hakone, Japan, 2007. AIDS Res Hum Retroviruses 23:597-598, 2007 (abstr 106)
22. Bazarbachi A, Panelatti G, Ramos JC, et al: A worldwide meta-analysis on the use of zidovudine and interferon-alpha for the treatment of adult T-cell leukemia/lymphoma: American Society of Hematology, Atlanta, Georgia, USA, 2007. Blood 110:610a-611a, 2007 (abstr 2049)
23. Bennett JM, Catovsky D, Daniel MT, et al: Proposals for the classification of chronic (mature) B and T lymphoid leukaemias: French-American-British (FAB) Cooperative Group. J Clin Pathol 42: 567-584, 1989
24. Gallamini A, Stelitano C, Calvi R, et al: Peripheral T-cell lymphoma unspecified (PTCL-U): A new prognostic model from a retrospective multicentric clinical study. Blood 103:2474-2479, 2004
25. Utsunomiya A, Hanada S, Terada A, et al: Adult T-cell leukemia with leukemia cell infiltration into the gastrointestinal tract. Cancer 61:824-828, 1988
26. Teshima T, Akashi K, Shibuya T, et al: Central nervous system involvement in adult T-cell leukemia/lymphoma. Cancer 65:327-332, 1990
27. Kamihira S, Atogami S, Sohda H, et al: Significance of soluble interleukin-2 receptor levels for evaluation of the progression of adult T-cell leukemia. Cancer 73:2753-2758, 1994
28. Sadamori N, Ikeda S, Yamaguchi K, et al: Serum deoxythymidine kinase in adult T-cell leukemia-lymphoma and its related disorders. Leuk Res 15:99-103, 1991
29. Itoyama T, Chaganti RS, Yamada Y, et al: Cytogenetic analysis and clinical significance in adult T-cell leukemia/lymphoma: A study of 50 cases from the human T-cell leukemia virus type-1 endemic area, Nagasaki. Blood 97:3612-3620, 2001
30. Oshiro A, Tagawa H, Ohshima K, et al: Identification of subtype-specific genomic alterations in aggressive adult T-cell leukemia/lymphoma. Blood 107:4500-4507, 2006
31. Tsukasaki K, Tsushima H, Yamamura M, et al: Integration patterns of HTLV-I provirus in relation to the clinical course of ATL: Frequent clonal change at crisis from indolent disease. Blood 89:948-956, 1997
32. Ramos JC, Ruiz P Jr, Ratner L, et al: IRF-4 and c-Rel expression in antiviral-resistant adult T-cell leukemia/lymphoma. Blood 109:3060-3068, 2007
33. Bazarbachi A, Ghez D, Lepelletier Y, et al: New therapeutic approaches for adult T-cell leukaemia. Lancet Oncol 5:664-672, 2004
34. Taylor GP, Matsuoka M: Natural history of adult T-cell leukemia/lymphoma and approaches to therapy. Oncogene 24:6047-6057, 2005
35. Yamada Y, Murata K, Kamihira S, et al: Prognostic significance of the proportion of Ki-67-positive cells in adult T-cell leukemia. Cancer 67:2605-2609, 1991
36. Tsukasaki K, Utsunomiya A, Fukuda H, et al: VCAP-AMP-VECP compared with biweekly CHOP for adult T-cell leukemia-lymphoma: Japan Clinical Oncology Group Study JCOG9801. J Clin Oncol 25:5458-5464, 2007
37. Tsukasaki K, Ikeda S, Murata K, et al: Characteristics of chemotherapy-induced clinical remission in long survivors with aggressive adult T-cell leukemia/lymphoma. Leuk Res 17:157-166, 1993
38. Gill PS, Harrington W Jr, Kaplan MH, et al: Treatment of adult T-cell leukemia-lymphoma with a combination of interferon alpha and zidovudine. N Engl J Med 332:1744-1748, 1995
39. Hermine O, Bouscary D, Gessain A, et al: Treatment of adult T-cell leukemia-lymphoma with zidovudine and interferon alfa. N Engl J Med 332: 1749-1751, 1995

40. Bazarbachi A, Hermine O: Treatment with a combination of zidovudine and alpha-interferon in naive and pretreated adult T-cell leukemia/lymphoma patients. J Acquir Immune Defic Syndr Hum Retrovirol 13:S186-S190, 1996 (suppl 1)

41. White JD, Wharfe G, Stewart DM, et al: The combination of zidovudine and interferon alpha-2B in the treatment of adult T-cell leukemia/lymphoma. Leuk Lymphoma 40:287-294, 2001

42. Matutes E, Taylor GP, Cavenagh J, et al: Interferon alpha and zidovudine therapy in adult T-cell leukaemia lymphoma: Response and outcome in 15 patients. Br J Haematol 113:779-784, 2001

43. Hermine O, Allard I, Levy V, et al: A prospective phase II clinical trial with the use of zidovudine and interferon-alpha in the acute and lymphoma forms of adult T-cell leukemia/lymphoma. Hematol J 3:276-282, 2002

44. Datta A, Bellon M, Sinha-Datta U, et al: Persistent inhibition of telomerase reprograms adult T-cell leukemia to p53-dependent senescence. Blood 108:1021-1029, 2006

45. Takasaki Y, Tsukasaki K, Iwanaga M, et al: A long-term study of prognosis in indolent types of adult T-cell leukemia/lymphoma (ATLL): 13th International Conference on Human Retrovirology, Hakone, Japan, 2007. AIDS Res Hum Retroviruses 23:597-598, 2007 (abstr 208)

46. Fukushima T, Miyazaki Y, Honda S, et al: Allogeneic hematopoietic stem cell transplantation provides sustained long-term survival for patients with adult T-cell leukemia/lymphoma. Leukemia 5:829-834, 2005

47. Okamura J, Utsunomiya A, Tanosaki R, et al: Allogeneic stem-cell transplantation with reduced conditioning intensity as a novel immunotherapy and antiviral therapy for adult T-cell leukemia/lymphoma. Blood 105:4143-4145, 2005

48. Yamaguchi K, Matutes E, Catovsky D, et al: Strongyloides stercoralis as candidate co-factor for HTLV-I-induced leukaemogenesis. Lancet 2:94-95, 1987

49. Gabet AS, Mortreux F, Talarmin A, et al: High circulating proviral load with oligoclonal expansion of HTLV-1 bearing T cells in HTLV-1 carriers with strongyloidiasis. Oncogene 19:4954-4960, 2000

50. Satoh M, Toma H, Sugahara K, et al: Involvement of IL-2/IL-2R system activation by parasite antigen in polyclonal expansion of CD4(+)25(+) HTLV-1-infected T-cells in human carriers of both HTLV-1 and *S. stercoralis*. Oncogene 21:2466-2475, 2002

51. Cheson BD, Horning SJ, Coiffier B, et al: Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas: NCI Sponsored International Working Group. J Clin Oncol 17:1244, 1999

52. Cheson BD, Bennett JM, Grever M, et al: National Cancer Institute-sponsored Working Group guidelines for chronic lymphocytic leukemia: Revised guidelines for diagnosis and treatment. Blood 87:4990-4997, 1996

53. Cheson BD, Pfistner B, Juweid ME, et al: The International Harmonization Project on Lymphoma: Revised response criteria for malignant lymphoma. J Clin Oncol 25:579-586, 2007

54. Bazarbachi A, El Sabban M, Nasr R, et al: Arsenic trioxide and interferon alpha synergize to induce cell cycle arrest and apoptosis in HTLV-I transformed cells. Blood 93:278-283, 1999

55. El-Sabban M, Nasr R, Dbaibo G, et al: Arsenic-interferon-alpha-triggered apoptosis in HTLV-I transformed cells is associated with Tax downregulation and reversal of NF-kappa B activation. Blood 96: 2849-2855, 2000

56. Nasr R, Rosenwald A, El-Sabban ME, et al: Arsenic/interferon specifically reverses two distinct gene networks critical for the survival of HTLV-I infected leukemic cells. Blood 101:4576-4582, 2003

57. Hermine O, Dombret H, Poupon J, et al: Phase II trial of arsenic trioxide and alpha interferon in patients with relapsed/refractory adult T-cell leukemia/lymphoma. Hematol J 5:130-134, 2004

58. Nasr R, El-Sabban M, Karam J, et al: Efficacy and mechanism of action of the proteasome inhibitor PS-341 in T cell lymphomas and HTLV-I associated adult T-cell leukemia/lymphoma. Oncogene 24: 419-430, 2005

59. El-Sabban M, Abu Merhi R, Abi Haidar H, et al: Human T-cell lymphotropic virus type I transformed cells induce angiogenesis and establish functional gap junctions with endothelial cells. Blood 99:3383-3389, 2002

60. Moura IC, Lepelletier Y, Arnulf B, et al: A neutralizing monoclonal antibody (mAb A24) directed against the transferring receptor induces apoptosis of tumor T lymphocytes from ATL patients. Blood 103:1838-1845, 2004

61. Pise-Masison CA, Radonovich MA, Dohoney KA, et al: Gene expression profiling of ATL Patients: Identification of signaling pathways which contribute to ATL—13th International Conference on Human Retrovirology, Hakone, Japan, 2007. AIDS Res Hum Retroviruses 23:597-598, 2007 (abstr 307)

