Human T-cell Lymphotropic Virus Type I–Associated Adult T-cell Leukemia–Lymphoma: New Directions in Clinical Research

Kunihiro Tsukasaki and Kensei Tobinai

Abstract

Adult T-cell leukemia–lymphoma (ATL) is a distinct malignancy of regulatory T cell (Treg)/TH2 cells caused by human T-cell lymphotropic virus type I (HTLV-1), with a high frequency of expression of CD3/CD4/CD25/CCR4 and FoxP3 in about half of the cells. However, in primary ATL cells, although expression of the virus, including the Tax oncoprotein, appears just after an in vitro culture, integration sites of the provirus into the host genome are random, and chromosomal/genetic abnormalities are complex. ATL is thus a single disease entity that is caused by HTLV-1 and possesses diverse molecular features. The clinical features and prognosis of ATL vary, and this has led to subtypes classified into four categories: acute, lymphomatous, chronic, and smoldering types, based on lactate dehydrogenase and calcium values and organ involvement. Approximately 15 to 20 million individuals are infected with HTLV-1 worldwide, 1.1 million of whom reside in Japan, and the annual incidence of ATL has been estimated to be approximately 1,000. HTLV-1 infection early in life, mainly from breast feeding, is crucial for the development of ATL. The age-specific occurrence of ATL and complex genome abnormalities that accumulate with disease progression suggest a multistep carcinogenesis model following HTLV-1 infection. Various treatment options are available for ATL and consist of watchful waiting for indolent ATL, intensive chemotherapy followed by allogeneic hematopoietic stem cell transplantation for aggressive ATL, and a combination of IFNα and zidovudine for ATL with leukemic manifestation. Several promising new agents, including an anti-CCR4 antibody, are currently undergoing clinical trials associated with translational research.

See all articles in this CCR Focus section, "Paradigm Shifts in Lymphoma."

Clin Cancer Res; 20(20); 5217–25. ©2014 AACR.

Introduction

Adult T-cell leukemia–lymphoma (ATL) is a rare T-cell malignancy associated with human T-cell lymphotropic virus type I (HTLV-1; refs. 1–5). Several inflammatory diseases have also been associated with HTLV-1, including tropical spastic paraparesis (TSP)/HTLV-1–associated myelopathy (HAM), infective dermatitis, and HTLV-associated uveitis (6–9). Endemic areas have been identified for the virus and these diseases, including southwestern Japan, the Caribbean islands, tropical Africa, South America, the Middle East, and northern Oceania. Only a small percentage of HTLV-1 carriers infected through breast feeding develop the disease, which suggests multistep carcinogenesis (10–12). The diversity of the clinical features and prognosis of patients with this disease has led to its classification into four categories: acute, lymphomatous, chronic, and smoldering types, based on lactate dehydrogenase (LDH) and calcium values and organ involvement (13, 14). Various treatment options are available for ATL and consist of watchful waiting for indolent ATL, intensive chemotherapy followed by allogeneic hematopoietic stem cell transplantation for aggressive ATL, and a combination of IFNα and zidovudine (IFN/AZT) for ATL with leukemic manifestation. ATL is more refractory to chemotherapy than other peripheral T-cell lymphomas (PTCL), but is relatively sensitive to potential HTLV-1–targeting therapies such as allo-HSCT and IFN/AZT (12). A recent phase II trial revealed that an anti-CC chemokine receptor (CCR4) antibody was effective against relapsed ATL (15). Furthermore, other promising new agents for PTCL, including ATL, are being developed. Recent advances in clinical and translational research on this disease, including molecular, epidemiologic, biologic, and therapeutic aspects, are summarized below.

Molecular Epidemiology of ATL

The seroprevalence of HTLV-1 was examined in 1,196,321 Japanese first-time blood donors between 2006 and 2007 (16). A total of 3,787 of them were confirmed to be positive
for the anti-HTLV-1 antibody. By applying a fitness curve to age ranges outside the blood donor age range, the present number of HTLV-1 carriers from age 0 to 99 years was estimated to be at least 1.08 million in Japan, approximately 10% lower than that reported in 1988. The adjusted overall prevalence rates of HTLV-1 were estimated to be 0.66% and 1.02% in men and women, respectively. Carrier numbers peaked among individuals in their 70s, markedly different from the previous peak observed among individuals in their 50s in the 1988 database, probably reflecting a birth cohort effect. Compared with the survey conducted in the 1980s, carriers were distributed not only in endemic regions in Japan, but throughout the country, particularly in the greater Tokyo metropolitan area (16). A high prevalence of HTLV-1 is also found in the Caribbean islands (African), tropical Africa (African), South America (Mongoloid), and northern Oceania (Melanesian; refs. 10, 11).

The three major routes of HTLV-1 transmission are mother-to-child infections (via breast milk), sexual intercourse, and blood transfusions (10, 11). The overall infection rate of HTLV-1 in children by seropositive mothers was previously estimated to be between 10% and 30% mainly through breast feeding (17). The reported risk factors for the development of ATL among HTLV-1 carriers include HTLV-1 infection early in life, an increase in age, male sex, family history of ATL, past history of infectious dermatitis, smoking, serum titters of the antibody against HTLV-1, HTLV-1 proviral load, and several HLA subtypes (11, 18). However, these were the findings of relatively small and not-comprehensive studies. A total of 1,218 asymptomatic HTLV-1 carriers (426 males and 792 females) were examined between 2002 and 2008 for a prospective cohort-study on the development of ATL in Japan (19). The proviral load at enrollment was significantly higher in males than in females [median, 2.1 vs. 1.4 copies/100 peripheral blood mononuclear cells (PBMC)], in those ages 40 or older, and in those with a family history of ATL. During the follow-up period, 14 participants developed acute ATL. Their baseline proviral loads were high (range, 4.2–28.6 copies/100 PBMC). Not only a higher proviral load, but also advanced age, family history of ATL, and the first opportunity for HTLV-1 testing during the treatment of other diseases were independent risk factors for the progression of ATL.

Although the incidence of ATL in HTLV-1–endemic areas is known to be high, population-based evidence concerning the incidence of ATL in nonendemic areas is scarce. Chihara and colleagues recently estimated the age-standardized incidence of ATL between 1993 and 2006 in Japan and between 1993 and 2008 in the United States, and assessed trends using a population-based cancer registry in Japan and Surveillance Epidemiology and End Results in the United States (20). A total of 2,055 patients in three prefectures in Kyushu and 1,380 patients in 12 prefectures in Honshu were diagnosed with ATL during the study period. In the United States, a total of 140 patients were diagnosed with ATL. This study showed that the age-standardized incidence in nonendemic areas in Japan and the United States significantly increased during this period (annual percentage change (95% confidence interval; CI); Japan-Honshu: +4.6% (1.1–8.2); U.S.: +6.2% (1.5–11.1)), whereas no change was observed in endemic areas in Japan (Japan-Kyushu: 0.0%; 1.6–1.7).

Biology of HTLV-1–Associated ATL

The HTLV-1 gene encodes three structural proteins: Gag, Pol, and Env, and complex regulatory proteins such as Tax, which not only activate viral replication, but also induce the expression of several cellular genes important in the proliferation and apoptosis of ATL cells, including NF-kB (Fig. 1; refs. 5, 21, 22). The expression of these cellular proteins may enhance the multistep carcinogenesis of ATL, whereas expression of the viral proteins in vivo is suppressed by cytokotic T cells. A new viral factor, HTLV-1 basic Zip factor (HBZ), which was encoded from the minus strand of mRNA, was recently discovered and may play a role in viral replication and T-cell proliferation because it is steadily expressed in most HTLV-1–infected cells and primary ATL cells whereas Tax is not (23). The polycomb-mediated epigenetic silencing of miR31 was more recently reported to be implicated in the aberrant and constitutive activation of NF-kB signaling in ATL cells (24). HBZ and miR31 may be good targets for the prevention as well as treatment of ATL.

ATL is a distinct malignancy of regulatory T cell (Treg)/TH2 cells caused by HTLV-1 with high frequency of expression of CD3/CD4/CD25/CCR4 and FoxP3 in about half of the cells (25, 26).

Figure 2 summarizes the multistep leukemogenesis of ATL, which consists of viral, epigenetic, and genetic factors. Regarding the viral factors, Tax, which is a strong transactivating factor of host genes and important in cell transformation, is considered to be crucial for the oligoclonal maintenance and expansion of HTLV-1–infected cells in the early phase of HTLV-1–infected individuals, the so-called healthy HTLV-1 carriers (10, 11, 22). However, the expression of Tax, which is very immunogenic, should be transient on each HTLV-1–infected cell escaping the immune surveillance of the host. Thereafter HTLV-1–infected cells can transform with a combination of the continued expression of HBZ, acquired epigenetic regulation of cell-transforming factors, full-blown development of ATL with the genetic/epigenetic loss of function of tumor suppressor genes and microRNAs (miRNA), and activation of oncogenes (12, 23, 24, 27–34). These abnormalities are acquired during the progression of ATL from the indolent to the aggressive subtypes. These abnormalities, excluding Tax, HBZ, and miR31, are very diverse, as revealed by the aneuploidy profile obtained using comparative genomic hybridization and microarray expression profile (35, 36). These findings indicated that ATL is a single disease entity associated with HTLV-1 that acquires diverse molecular abnormalities resembling the acute-crisis phase of chronic myeloid leukemia with similar diverse abnormalities caused by bcr/abl. Clonal selection during the progression of ATL is typically the consequence of clonal evolution.
Multiple subclones in lymph nodes originate from a common clone in many ATL cases, and a selected subclone among the lymph node subclones appears in the peripheral blood (37). Clonal changes, but not clonal evolution, have been reported in approximately 10% of cases progressing from indolent to acute ATL, and may reflect the emergence of multiple premalignant oligoclonal to viral leukemogenesis, as suggested in Epstein–Barr virus-associated lymphomagenesis in immunocompromised hosts (38, 39). The genomic characteristics of proviral integration sites in malignant and nonmalignant clones, as well as the proviral features (genomic structure and 5′ LTR methylation) that determine its capacity to express Tax, were recently identified using a sensitive high-throughput method for primary ATL cells (40).

ATL lesions in the peripheral blood are morphologically diagnosed in the same manner as other lesions involving the lymph nodes (13, 14). However, ATL cell atypia vary from the so-called flower cells with multilobulated nuclei to chronic lymphocytic leukemia (CLL)–like cells resembling normal lymphocytes (41). The monoclonal integration of HTLV-1 detected by Southern blotting hybridization (SBH) is used as a supportive method for the diagnosis of ATL with a threshold sensitivity of approximately 5%. However, SBH can also detect monoclonal integration in a small percentage of HTLV-1 carriers and approximately 10% of HAM/TSP patients (42, 43). Flow-cytometric analysis of T cells recently revealed that the expression of CADM1 and stepwise down-regulation of CD7 were closely associated with the clonal expansion of HTLV-1–infected cells in ATL, and CADM1+ cells with the downregulated expression of CD7 in asymptomatic HTLV-1 carriers exhibited common properties to those in indolent ATL carriers (44).

Treatment and Prognosis of ATL

The prognosis of ATL is worse than that of other PTCLs (45). The clinical subtype classification of ATL is very useful for decision making about the treatment of each patient (13). However, there is no plateau—rather an initial steep slope and subsequent gentle slope in the survival curves of aggressive and indolent ATL treated with chemotherapy and watchful waiting, respectively, although the prognosis of the latter is markedly better [median survival time (MST), 1 year vs. 5 years; refs. 13, 46]. Improved prognostic systems have been sought. From North America, a new prognostic score for ATL was reported, based on performance status (PS), stage, age, and calcium level at diagnosis (47). A recent retrospective survey in Japan on 807 patients with acute or lymphomatous ATL treated with chemotherapy, but not with allo-HSCT, developed a prognostic index based on five prognostic factors: stage, PS, age, serum albumin, and soluble IL2 receptor (48). In the validation sample, the index was reproducible with MSTs of 3.6, 7.3, and 16.2 months for patients at high, intermediate, and low risk, respectively. The Japan Clinical Oncology Group (JCOG)-Lymphoma Study Group (LSG) conducted a meta-analysis of three consecutive trials exclusively for aggressive ATL (see below; ref. 49). An overall survival (OS) analysis of 276 patients with aggressive ATL identified two significant prognostic factors, PS and hypercalcemia. In the validation sample, a proposed prognostic index using these two factors...
in two strata revealed MSTs of 6.3 and 17.8 months for patients at high and low risk, respectively. However, the 5-year OS rates in both studies were less than 15%, even in the low-risk group; therefore, the subgroup with relatively favorable prognoses could not be identified. However, approximately 10% of patients with lymphoma-type ATL survived more than 10 years without allo-HSCT, which suggests that they may have been cured (49).

JCOG-LSG has consecutively conducted clinical trials on aggressive non-Hodgkin lymphoma (NHL), including ATL (50). Aggressive ATL has been exclusively studied from other NHLs after far worse response and survival rates were reported in earlier studies. A phase II trial (JCOG9303) for aggressive ATL using the LSG15 regimen, which consisted of six cycles of vincristine, cyclophosphamide, doxorubicin, and prednisone (VCAP); doxorubicin, ranimustine, and prednisone (AMP); and vindesine, etoposide, carboplatin, and prednisone (VECP) with the prophylactic use of G-CSF and intrathecal prophylaxis, revealed a promising response rate and MST. After JCOG9303, we conducted a phase III trial to compare modified (m)-LSG15 (VCAP-AMP-VECP) with CHOP-14, both supported by G-CSF and intrathecal prophylaxis. A higher 3-year survival rate (24% vs. 13%) and complete response rate (40% vs. 25%) with mLSG15 than with CHOP-14 suggested that the former was a more effective regimen at the expense of greater toxicities, which provided the basis for future investigations on the treatment of aggressive ATL (51). However, the MST of 13 months is still unsatisfactory.

A treatment strategy for ATL based on clinical subtypes, prognostic factors, and response to the initial therapy was suggested in an international consensus report (52). Patients with aggressive ATL generally have a very poor prognosis due to the multidrug resistance of ATL cells, large tumor burden with multiorgan failure, hypercalcemia, and/or opportunistic infections (10–13). Intensive chemotherapy such as mLSG15 is recommended for aggressive ATL (51, 52). Watchful waiting until disease progression has been recommended for indolent ATL, although the long-term prognosis of this disease was inferior to that of, for example, CLL (46, 52). 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, stage, number of involved lesions, and hypercalcemia, and molecular factors, such as Ki-67 expression, soluble IL2 receptor,
alteration of p53 or p15INK4B/p16INK4A, and overexpression of IRF-4 (47–49, 52). Initial relatively small phase II studies and recent retrospective meta-analyses suggested that IFN/AZT therapy may be promising, especially for types with leukemic manifestation (53–55). The therapeutic effects of IFN/AZT are not considered to be attributable to direct cytotoxic effects on leukemic cells (56). A possible mechanism of the combination for ATL includes AZT treatment of ATL cell lines resulting in telomere attrition, which reprograms cells to undergo p53-dependent senescence, and IFN alone suppressing the expression of HTLV-1 and cell cycling, whereas IFN/AZT induces p53 signaling and apoptosis in HTLV-1–infected cells (57, 58).

Allo-HSCT is promising for the treatment of aggressive ATL, possibly reflecting graft-versus-ATL effect, including the nonmyeloablative conditioning regimen (59–61). Minimal residual disease following allo-HSCT, which is detected as the HTLV-1 proviral load, was markedly less than that after chemotherapy or AZT/IFN therapy, which suggested the presence of a graft-versus-ATL effect as well as graft-versus-HTLV-1 activity (62). ATL with abnormalities in tumor suppressor genes such as p53 was reportedly resistant to IFN/AZT therapy as well as chemotherapy. Allo-HSCT may overcome this resistance (52). It remains unclear which type of allo-HSCT (myeloablative or reduced-intensity conditioning) is more suitable for the treatment of ATL. Furthermore, selection criteria with respect to responses to previous treatments, the sources of stem cells, and the HTLV-1 viral status of the donor have yet to be determined.

### Table 1. Strategy for the treatment of adult T-cell leukemia–lymphoma proposed from an international consensus meeting

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

Abbreviation: CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone.


Translational Research and Clinical Trials of New Agents for ATL

Translational research is mandatory for the development of new agents against specific disease subtypes such as PTCLs, including ATL. Research on the biology of HTLV-1–infected cells and ATL cells revealed that the II.2, II.9, II.15...
Histone deacetylase inhibitors

Gene expression governed by epigenetic changes is crucial to the pathogenesis of cancer. Histone deacetylases are enzymes that are involved in the remodeling of chromatin, and play a key role in the epigenetic regulation of gene expression. The histone deacetylase inhibitor (HDACi) LBH589 exhibits significant anti-ATL effects by activating expression modulation of ATL-related proteins, including Tax and CCR4 (68). However, a phase II study of LBH589 for CTCL and indolent ATL was terminated because of severe infections associated with the shrinkage of skin tumors and formation of ulcers in patients with ATL. Romidepsin, another HDACi, was recently approved for the treatment of relapsed/refractory ATL by the FDA. Further studies are needed to evaluate the efficacy of HDACis for PTCL/cutaneous T-cell lymphoma (CTCL), including ATL.

Proteasome inhibitors

The proteasome inhibitor bortezomib suppresses the activation of NF-κB, which is constitutively expressed in all subtypes of ATL cells and HTLV-1-infected cells, and has been implicated in oncogenesis as well as resistance to anticancer agents and apoptosis. This agent effectively inhibits the growth of ATL cells both in vivo and in vitro (69). A phase II study of bortezomib is now ongoing for ATL in Japan.

CD30-directed antibody–drug conjugates

The TNF receptor family member CD30 is an activation marker of lymphocytes, and signaling through CD30 is associated with cell proliferation. Some PTCLs, including ATL, as well as Hodgkin lymphoma and anaplastic large-cell lymphoma (ALCL), express CD30. Most ATL cells in less than 10% of ATL cases express CD30, similar to ALCL, whereas several to 10% of ATL cells express CD30 in the remaining ATL cases (14). To enhance the antitumor activity of CD30-directed therapy, the antitubulin agent monomethyl auristatin E was attached to a CD30-specific mAb by an enzyme-cleavable linker to produce the antibody–drug conjugate brentuximab vedotin (SGN-35). Brentuximab vedotin induced durable objective responses with acceptable toxicities in most patients with relapsed or refractory CD30-positive Hodgkin lymphoma/ALCL in several phase I and II studies (70). Regarding newly diagnosed CD30-positive PTCLs, including ATL, a phase I study of brentuximab vedotin + CHP, in which VCR was omitted to avoid its additive neurotoxicity, revealed promising results (71).

Anti-CCR4 antibody

CCR4 is expressed on the neoplastic cells of most patients with ATL, and this expression has been associated with the cutaneous manifestation and poor prognosis. The aberrant expression of Fra-2 promotes that of CCR4 and cell proliferation in ATL cells (72). The defucosylated humanized anti-CCR4 mAb (mogamulizumab), the ADCC activity of which was stronger than that of the usual antibody in preclinical analysis using primary ATL and effector cells, was approved for the treatment of relapsed/refractory ATL in Japan based on the results of phase I and II studies, with a response rate of approximately 50% and manageable toxicities, including moderate to severe skin reactions (15, 73, 74). The findings of a subsequent randomized phase II study on intensive chemotherapy (mLG15) ± mogamulizumab for untreated aggressive ATL have recently been reported (75). This combination was anticipated because the former was more effective for ATL cells in lymph nodes than those in the peripheral blood, whereas the opposite was true for the latter (15, 51). The combination was well tolerated and produced a higher complete response rate [52% (95% CI, 33–71) vs. 33% (CI, 16–55)], respectively. Clinical trials of mAbs for ATL and other PTCLs include a humanized anti-CD52 mAb (alemtuzumab) and a humanized anti-CD2 mAb (sipilizumab).

Other new agents

Other new agent trials for ATL and/or PTCL that are ongoing or in preparation in Japan include studies of IL2 fused with the diphtheria toxin targeting CD25; a novel purine nucleoside phosphorylase inhibitor, forodesine; an anti-folate, pralatrexate, an FDA-approved agent with clinical activity in T-cell malignancies, including ATL; an organic arsenic; and the immunomodulatory agent lenalidomide (76).

Conclusions

ATL cases are separately treated on the basis of the aggressive-versus-indolent subtypes, with prompt treatment using combination chemotherapy, followed by
allo-HSCT versus watchful waiting until disease progression, respectively. Therefore, future issues to be resolved in the treatment of this intractable disease with diverse clinical features include new standard treatments between watchful waiting and intensive chemotherapy ± allo-HSCT. IFN/AZT and mogamulizumab are promising treatment options, especially for aged patients. Another aspect is multimodality treatments for ATL with an extremely poor prognosis.

Two prospective studies are ongoing for ATL by JCOG-LSG. One is a Phase II study of mLSG15 and mogamulizumab followed by allo-HSCT with myeloablative or non-myeloablative conditioning for aggressive ATL (JCOG0907). The other is a Phase III trial for indolent ATL to compare IFN/AZT with watchful waiting (JCOG1111).

Furthermore, as described in more detail in the CCR Focus article by O’Connor and colleagues, more than 10 promising new agents for PTCL/CTCL, including ATL, are undergoing clinical trials or are in preparation with translational research. Future clinical trials on ATL should be carefully and appropriately conducted to ensure that the international consensus on ATL management is continually updated to establish evidence-based practical guidelines.

Disclosure of Potential Conflicts of Interest
K. Tsukasaki reports receiving commercial research grants from Celgene, Kyowa-Kirin, and Takeda. K. Tobinai reports receiving commercial research grants from Celgene, Kyowa-Kirin, Mundipharma, and Takeda. No other potential conflicts of interest were disclosed.

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Conception and design: K. Tsukasaki, K. Tobinai
Development of methodology: K. Tobinai
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): K. Tsukasaki, K. Tobinai
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Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): K. Tsukasaki, K. Tobinai
Study supervision: K. Tobinai

Grant Support
This work was supported in part by the National Cancer Center Research and Development Fund (23-A-17 and 26-A-4; to K. Tsukasaki and K. Tobinai).

Received May 19, 2014; revised August 4, 2014; accepted August 20, 2014; published online October 15, 2014.

References


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