Adult T cell Leukemia-Lymphoma

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Abstract

Adult T-cell leukemia–lymphoma (ATL) was first described in 1977 as a distinct clinico-pathological entity with a suspected viral etiology. Subsequently, a novel RNA retrovirus, human T-cell leukemia/lymphotropic virus type 1 (HTLV-1) was isolated from a cell line established from the leukemic cells of an ATL patient, and the finding of a clear association with ATL led to its inclusion among human carcinogenic pathogens. The three major routes of HTLV-1 transmission are mother-to-child infections via breast milk, sexual intercourse, and blood transfusions. HTLV-1 infection early in life, presumably from breast feeding, is crucial in the development of ATL. The diversity in clinical features and prognosis of patients with this disease has led to its subtype-classification into four categories, acute, lymphoma, chronic, and smoldering types defined by organ involvement, and LDH and calcium values. In case acute, lymphoma or unfavorable chronic subtypes (aggressive ATL), intensive chemotherapy such as VCAP-AMP-VECP is usually recommended. In case favorable chronic or smoldering ATL (indolent ATL), watchful waiting until disease progression has been recommended although the long term prognosis was inferior to those of, for instance, chronic lymphoid leukemia. Retrospective analysis suggested that the combination of interferon alpha and zidovudine was apparently promising for the treatment of ATL, especially for types with leukemic manifestation. Allogeneic hematopoietic stem cell transplantation is also promising for the treatment of aggressive ATL possibly reflecting graft vs. ATL effect. Several new agent-trials for ATL are ongoing and in preparation, including a defucosylated humanized anti-CC chemokine receptor 4 monoclonal antibody. Two steps should be considered for the prevention of HTLV-1-associated ATL. The first is the prevention of HTLV-1 infections and the second is the prevention of ATL among HTLV-1 carriers. So far, no agent has been found to be effective for the latter. Further investigation on the pathogenesis of ATL is crucial for the prevention and treatment of this refractory leukemia–lymphoma.

Adult T-cell leukemia-lymphoma (ATL) was first described in 1977 by Uchiyama, Takatsuki, et al as a distinct clinico-pathological entity with a suspected viral etiology because of the clustering of the disease in the southwest region of Japan [1]. Subsequently, a novel RNA retrovirus, human T-cell leukemia/lymphotropic virus type I (HTLV-1), was isolated from a cell line established from leukemic cells of an ATL patient, and the finding of a clear association with ATL led to its inclusion among human carcinogenic pathogens [2-5]. In the mid-1980s and 1990s, several inflammatory diseases were reported to be associated with HTLV-1 including tropical spastic paraparesis (TSP)/HTLV-1-associated myelopathy (HAM), HTLV-associated uveitis and infective dermatitis. [6-9] At the same time, endemic areas for the virus and diseases have been found such as the Caribbean basin, parts of Africa, Latin America, the Middle East and the Pacific region.

The three major routes of HTLV-1 transmission are mother-to-child infections via breast milk, sexual intercourses and blood transfusions. The overall infection rate of HTLV-1 in children by seropositive mothers has been estimated to be 10% to 30%. It was estimated that approximately 1.2 million HTLV-1–infected individuals reside in Japan, and the annual incidence of ATL to be approximately 1000 in 1990s. The cumulative life time risk for ATL among HTLV-1 carriers has been estimated at 1-5% with a median age of about 60 years old in Japan. Patients in areas outside Japan are somewhat younger, with an overall mean age in the mid-40s. The age-specific occurrence of ATL suggested a multistep carcinogenesis model. HTLV-1 infection early in life, presumably from breast feeding, is crucial in the development of ATL.

ATL is etiologically associated with HTLV-1. However, HTLV-1 does not carry viral oncogene, expression of the virus including Tax appears just after in vitro culture, integration sites of the provirus into host genome is random, and chromosomal/genetic abnormality is complex. Therefore, ATL is a single HTLV-1 disease entity with diverse molecular features. Also, the clinical features and prognosis of patients with this disease is diverse leading to subtype-classification into four categories, acute, lymphoma, chronic, and smoldering types defined by organ involvement, and LDH and calcium values (Table 1) [10,11].

The HTLV-I gene encodes three structural proteins, Gag, Pol and Env, and complex regulatory proteins such as Tax, which not only activate viral replication but also induces the expression of several cellular genes. The expression of these cellular proteins may enhance the multistep carcinogenesis of ATL. Recently, a new viral factor, HTLV-1 basic Zip factor (HBZ), encoded from the minus strand mRNA was discovered and is thought to be implicated in viral replication and T-cell proliferation. Several

isoforms of HBZ transcripts were reported to be steadily expressed in HTLV1–infected cells and primary ATL cells in contrast to Tax. The functions of these transcripts and putative protein in the context of cellular transformation are now under investigation.

Prototypical ATL cells have a mature helper T-cell phenotype (CD3+, CD4+, CD8-). Recent studies have suggested that the cells of some ATL may be the equivalent of regulatory T-cells because of the high frequency of expression of CD25/CCR4 and about half of FoxP3. The tumor suppressor genes such as p53, p14/p16 and an apoptosis-signaling cell surface receptor, Fas, are often abnormal in aggressive ATL. By Southern blotting for both HTLV-1 integration and TCR rearrangement, about 10-20% of ATL cases showed clonal change during the transformation from indolent to aggressive disease. Oligoclonal expansion of HTLV-1 infected pre-malignant cells was detected in asymptomatic HTLV-1 carriers by HTLV-1 integrated site specific PCR. A high rate of chromosomal abnormalities has been detected in HTLV-1-infected T-cell clones derived from HTLV-1 carriers. Abnormalities in tumor suppressor genes are frequent and rare in acute- and chronic-type ATL, respectively and associated in poor prognosis in both. Chromosomal abnormalities detected by cytogenetics or comparative genomic hybridization are often more complex and more frequent in acute ATL than in chronic ATL, with aneuploidy and several hot spots such as 14q and 3p. DNA microarray analyses of the transcriptomes of ATL cells at the chronic and acute stages to elucidate the mechanism of stage progression in this disease revealed that several hundred genes were modulated in expression including those for MET, a receptor tyrosine kinase for hepatocyte growth factor and cell adhesion molecule, TSLC1.

Definitive risk factors for the development of ATL among asymptomatic HTLV-1 carriers remain unclear. HTLV-1 proviral loads have been proposed as an important predictor of ATL, but only a few small prospective studies have been conducted. Recently, we evaluated 1,218 asymptomatic HTLV-1 carriers (426 males and 792 females) who were enrolled during 2002–2008 for a prospective study on the development of ATL in Japan. The proviral load at enrollment was significantly higher in males than females (median, 2.1 vs. 1.4 copies/100 peripheral blood mononuclear cells (PBMC), in those aged 40 or more years, 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). Multivariate Cox regression analyses indicated that not only a higher proviral load but also advanced age, a family history of ATL, and the first opportunity for HTLV-1 testing during treatment for other diseases were independent risk factors for the progression of ATL from a carrier status.

Major prognostic indicators for ATL, which have been elucidated in 854 patients with ATL in Japan by multi-variate analysis, were advanced performance status, high LDH level, age of 40 years or more, more than 3 involved lesions, and hypercalcemia. Additional factors reportedly associated with a poor prognosis include thrombocytopenia, eosinphilia, bone marrow involvement, a high interleukin-5 serum-level, C-C chemokine receptor 4 (CCR4) expression, lung resistance-related protein (LRP), p53 mutation and p16 deletion by multivariate analysis. Specific for the chronic type of ATL, high LDH, high blood urea nitrogen (BUN), and low albumin levels were identified as factors for a poor prognosis by multi-variate analysis. Primary cutaneous tumoral type although generally included among smoldering ATL had a poor prognosis in one uni-variate analysis.

Recently, a treatment strategy based on the clinical subtype classification and prognostic factors was suggested [11]. The chronic or 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 acute or lymphoma subtypes generally have a very poor prognosis despite chemotherapies such as CHOP probably due to multidrug-resistance of ATL cells, a large tumor burden with multi-organ failure, hypercalcemia and/or frequent infectious complications due to a profound T-cell immunodeficiency. In case acute, lymphoma or unfavorable chronic subtypes (aggressive ATL), intensive chemotherapy like the LSG15 regimen (VCAP-AMP-VECP) is usually recommended, if outside of clinical trials, based on the results of our recent phase 3 trial, Japan Clinical oncology Group (JCOG) 9801. In case favorable chronic or smoldering ATL (indolent ATL), watchful waiting until disease progression has been recommended although the long term prognosis was inferior to those of, for instance, B-CLL. Retrospective analysis from Europe, southern- and mid-America and USA suggested that the combination of interferon alpha and zidobudine was apparently promising for the treatment of ATL, especially for indolent type with leukemic and cutaneous manifestation. Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is also promising for the treatment of aggressive ATL possibly reflecting graft vs ATL effect.

Several new agent-trials for ATL are ongoing and in preparation in Japan, including a defucosylated humanized anti-CC chemokine receptor 4 monoclonal antibody, IL2-fused with diphtheria toxin, histone deacetylase inhibitors, a purine nucleoside phosphorylase inhibitor and lenalidomide.

Two steps should be considered for the prevention of HTLV-1-associated ATL. The first is the prevention of HTLV-1 infections. This has been achieved in some endemic areas by screening for HTLV-1 among blood donors and asking mothers who are carriers to refrain from breast feeding. The second step is the prevention of ATL among HTLV-1 carriers. This has not been achieved partly because only about 5 % of HTLV-1 carriers develop the disease in their life time although several risk factors have been identified. Also, no agent has been found to be effective in preventing the development of ATL among HTLV-1 carriers. Further investigation on the pathogenesis of ATL is crucial for the development of prevention and treatment of this refractory leukemia-lymphoma.

Reference

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Table1. Diagnostic Criteria for Clinical Subtypes of Adult T-Cell Leukemia-Lymphoma

	Smoldering	Chronic	Lymphoma	Acute
Anti-HTLV-I antibody	+	+	+	+
Lymphocyte (×10^3/μL)	<4	>=4‡	<4	*
Abnormal T lymphocytes	>=5%¶	+§	=<1%	+???
Flower cells with T-cell marker	†	†	No	+
LDH	=<1.5N	=<2N	*	*
Corrected Ca^{2+} (mEq/L)	<5.5	<5.5	*	*
Histology-proven Lymphadenopathy	No	*	+	*
Tumor lesionA	*	*	*	*
Skin and/or lung	*	*	*	*
Lymph node	No	*		*
Liver	No	*	*	*
Spleen	No	*	*	*
Central nervous system	No	*	*	*
Bone	No	No	*	*
Ascites	No	No	*	*
Pleural effusion	No	No	*	*
Gastrointestinal tract	No	No	*	*

HTLV-I, human T-lymphotropic virus type I; LDH, lactate dehydrogenase; N normal upper limit.

*No essential qualifi cation except terms required for other subtype(s).

†Typical “fl ower cells” may be seen occasionally.

‡Accompanied by T lymphocytosis (3.5 × 103/μL or more).

§If abnormal T lymphocytes are less than 5% in peripheral blood, histologically proven tumor lesion is required.

¶Histologically proven skin and/or pulmonary lesion(s) is required if there are fewer than 5% abnormal T lymphocytes in peripheral blood.

From Shimoyama M, Members of the Lymphoma Study Group (1984–1987): Diagnostic criteria and classifi cation of clinical subtypes of adult T-cell leukemia-lymphoma. Br JHaematol 1991;79:428.

Table2. Strategy for the treatment of Adult T-Cell Leukemia-Lymphoma

Smoldering- or favorable chronic-type ATL

- **Consider inclusion in prospective clinical trials**
- **Symptomatic patients (skin lesions, opportunistic infections, etc): Consider AZT/IFN or Watch and Wait**
- **Asymptomatic patients: Consider Watch and Wait**

Unfavorable chronic- or acute-type ATL

- **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 phase III trial against biweekly-CHOP) or AZT/IFN (evaluated by a meta-analysis on retrospective studies)**
  - **Poor prognostic factors: consider chemotherapy followed by conventional or reduced intensity allo-HSCT (evaluated by retrospective and prospective Japanese analyses, respectively).**
  - **Poor response to initial therapy: Consider conventional or reduced intensity allo-HSCT**

Lymphoma-type ATL

- **If outside clinical trials, consider chemotherapy (VCAP-AMP-VECP)**
- **Check prognostic factors (including clinical and molecular factors if possible) and response to chemotherapy:**
  - **Good prognostic factors and good response to initial therapy: Consider chemotherapy followed by observation**
  - **Poor prognostic factors or poor response to initial therapy: Consider chemotherapy followed by conventional or reduced intensity allo-HSCT.**