Prevention of Human T-Cell Lymphotropic Virus Type 1 Infection and Adult T-Cell Leukemia/Lymphoma

Makoto Yoshimitsu, Yohann White and Naomichi Arima

Abstract

Adult T-cell leukemia/lymphoma (ATLL) is a highly aggressive peripheral T-cell malignancy that develops after long-term chronic infection with human T-cell lymphotropic virus type-1 (HTLV-1). Despite the recent advances in chemotherapy, allogeneic hematopoietic stem cell transplantation (alloHSCT), and supportive care, the prognosis for patients with ATL is one of the poorest among hematological malignancies; overall survival (OS) at 3 years is only 24 % in the more aggressive subtypes of ATLL. HTLV-1 is a human retrovirus infecting approximately 10–20 million people worldwide, particularly in southern and southeastern Japan, the Caribbean, highlands of South America, Melanesia, and Equatorial Africa. Despite this high frequency of human infection, only 2–5 % of HTLV-1-infected individuals develop ATLL. Three major routes of viral transmission have been established: (1) mother-to-child transmission through breast-feeding; (2) sexual transmission, predominantly from men to women; and (3) cellular blood components. Multiple factors (e.g., virus, host cell, and immune factors) have been implicated in the development of ATLL, although the underlying mechanisms of leukemogenesis have not been fully elucidated. No preventive vaccine against HTLV-1 is currently available, and interrupting the well-recognized primary modes of HTLV-1 transmission is the mainstay of ATLL prevention. Prevention of

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mother-to-child transmission through the replacement of breast-feeding has been shown to have the most significant impact on the incidence of HTLV-1 infection, and public health policies should consider the risk of malnutrition, especially in developing countries where malnutrition is the significant cause of infant mortality.

Keywords
HTLV-1 · ATLL · ATL · Breast-feeding · Transfusion

Contents

1 Introduction of Prevention of HTLV-1 and Adult T-Cell Leukemia/Lymphoma

Human T-cell lymphotropic virus type 1 (HTLV-1) was first discovered as the human retrovirus causally linked to the T-cell hematological malignancy and adult T-cell leukemia/lymphoma (Poiesz et al. 1980; Yoshida et al. 1982). The virus is transmitted through contact with body fluids containing HTLV-1-infected cells, mostly from mother-to-child transmission through breast-feeding or through blood transfusions. Adult T-cell leukemia/lymphoma (ATLL) develops after a prolonged

incubation period in a minority of individuals infected with HTLV-1, and strategies aimed at preventing ATLL are based on interrupting HTLV-1 transmission. Firstly, interrupting HTLV-1 transmission by screening for HTLV-1 among blood donors and restricting breast-feeding by mothers who are HTLV-1 carriers have been the primary public health approaches in HTLV-1 endemic areas. The second strategy, although intuitive but that has yet to be realized due to a lack of effective modalities, is the prevention of progression to ATLL among HTLV-1 carriers. Approximately 90 % of HTLV-1 carriers remain as healthy uninfected individuals throughout their lifetime, and there are no clear predictors of progression to ATLL. In addition, preventive strategies such as vaccination could theoretically lead to preventive strategies based on our current understanding of immune-mediated disorders also known to be linked to HTLV-1, including HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP).

2 Epidemiology of HTLV-1 Infection

2.1 Worldwide

Nearly 20 million people worldwide are estimated to be infected with HTLV-1 (de The and Kazanji 1996). Among them, only less than 10 % develops HTLV-1-related disorders, including adult T-cell leukemia/lymphoma throughout their lifetime. A number of studies investigating the geographical and ethno-epidemiological distribution of the virus have been conducted over the last 3 decades (Goncalves et al. 2010; Sonoda et al. 2011) and have revealed that southwestern Japan, parts of Africa, the Caribbean Islands, and Central and South America are the endemic areas. In Europe and North America, infection with HTLV-1 is predominantly found in immigrant populations originating from endemic countries.

2.2 Japan

A recent seroprevalence study has revealed that the estimated number of HTLV-1 carriers in Japan is at least 1.08 million (Satake et al. 2012). This is 10 % lower than that reported in 1988. The estimated prevalence rates were 0.66 % in men and 1.02 % in women.

3 Mode of Transmission and Clinical Outcome

The primary modes of infection with HTLV-1 have been well described; namely (1) mother-to-child transmission, mainly via breast-feeding (Kinoshita et al. 1987; Yamanouchi et al. 1985); (2) sexual transmission, predominantly from men to women (Murphy et al. 1989; Tajima et al. 1982); and (3) through cellular blood

components (Okochi and Sato 1984). Studies suggest an association between the mode of infection and the type of HTLV-1-associated disease seen. ATLL has been mainly associated with acquiring infection through breast-feeding, and HAM/TSP with acquiring infection through blood transfusions (Osame et al. 1990). Reports of ATLL cases occurring in patients infected through blood transfusion are few (Chen et al. 1989). The risk of transmission from mother to child during breast-feeding has been estimated to be 20 % (Hino et al. 1985), while the risk of transmission during pregnancy or the peripartum period was estimated to be less than 5 % (Fujino and Nagata 2000). ATLL development may be linked to a prolonged period of infection with HTLV-1 acquired through vertical transmission.

4 Epidemiology of Adult T-Cell Leukemia/Lymphoma

Only a small proportion of HTLV-1 carriers develop ATLL after a long latency period. Despite the wide geographical distribution, data on the incidence and prevalence of ATLL, except for Japan, are scarce. Furthermore, it is likely that existing reports may be underestimating the prevalence of lymphoma subtype especially due to similarities in clinical presentation compared with other T-cell lymphomas and limited diagnostic capabilities in resource-poor settings. Among the Japanese population, the incidence of ATLL among carriers is estimated to be between 4.5 and 7.3 % in men and 2.6 and 3.5 % in women (Koga et al. 2010; Kondo et al. 1989; Tokudome et al. 1989). ATLL is reported to develop among individuals predominantly in their fifth decade of life in Japan (Takatsuki et al. 1996), whereas in Jamaica and Brazilian series, patients tend to present with the disease in the fourth decade of life, suggesting that other immunological or host genetic factors may play a role in the pathogenesis of ATLL (Gibbs et al. 1987; Pombo de Oliveira et al. 1995).

5 Mechanisms of HTLV-1 Transmission

HTLV-1 can infect a wide variety of human cell types in vitro (Koyanagi et al. 1993; Sommerfelt et al. 1988), and its presumed receptor is therefore thought to be a widely expressed molecule. Glucose transporter-1 (GLUT1), heparin sulfate proteoglycan (HSPG), and neuropilin-1 have been reported to be involved in the interaction between the viral envelop and the host cell membrane, and for viral entry into the target cells (Jones et al. 2005; Lambert et al. 2009; Manel et al. 2003). The current model postulates that HTLV-1 particles first come into contact with HSPG, followed by recruitment of the HTLV-1/HSPG complex by neuropilin-1, finally interacting with GLUT1. Formation of the HSPG/neuropilin-1/GLUT1 complex appears to be essential for the fusion of the viral envelope and host cell membrane and viral entry.

Cell-free HTLV-1 virions are poorly infectious in vitro for most of cell types, including their primary target cells, CD4 T-cells. Direct cell-to-cell contact appears to be essential for HTLV-1 infection, except for myeloid and plasmacytoid

dendritic cells (DCs), which appear to be susceptible to infection by cell-free HTLV-1 virions (Jones et al. 2008). DCs may therefore play an important role in transmission, possibly facilitating spread during contact between breast milk and the infant's gastrointestinal mucosa.

Three major mechanisms of cell-to-cell transmission of HTLV-1 have been proposed: (1) HTLV-1-infection of lymphocytes results in polarization of their microtubules and viral components upon contact with other T-cells, forming a so-called virological synapse (Igakura et al. 2003); (2) HTLV-1-infected cells produce and transiently store viral particles in extracellular adhesive structures rich in extracellular matrix components, including collagen and agrin, and cellular linker proteins, such as tetherin and galectin-3, similar to bacterial biofilms. Extracellular viral assemblies then rapidly adhere to other cells upon contact, allowing viral spread and infection of target cells (Pais-Correia et al. 2010); and (3) the HTLV-1–pX region-encoded p8 protein increases T-cell conjugation through lymphocyte function-associated antigen-1 clustering. In addition, p8 induces cellular conduits among T-cells and increases viral transmission (Van Prooyen et al. 2010).

6 Prevention of Transmission of HTLV-1

The prognosis for ATLL remains one of the worst among hematological malignancies, even with the best available therapies, and no preventive vaccine against HTLV-1 is currently available. Prevention of transmission of HTLV-1 is therefore an important strategy in preventing ATLL.

6.1 Prevention of Vertical Transmission

Based on retrospective and prospective epidemiological studies, the mother-to-child transmission rate is estimated to be 20 % (Hino et al. 1985). Prevention of mother-to-child transmission by restricting breast-feeding has the most significant impact on the incidence of HTLV-1 infection and associated diseases. In a prefecture-wide intervention study in Nagasaki, southern Japan, in which mothers with HTLV-1 infection were counseled to avoid breast-feeding, there was a marked reduction of mother-to-child transmission from 20.3 to 2.5 %. Thus, prenatal screening for HTLV-1 may be an important public health strategy in endemic areas, in conjunction with counseling of mothers with HTLV-1 infection to avoid breast-feeding. Although children breast-fed for less than 6 months have significantly lower incidence of HTLV-1 infection than those breast-fed for more than 6 months, the risk of transmission is significantly higher for the former group compared with formula-fed infants (Hino 2011).

Even with exclusive bottle-feeding, 2.5 % of infants born to carrier mothers become infected with HTLV-1. As intrauterine transmission of HTLV-1 is rare, transplacental transmission during delivery seems to be the probable mode of transmission, as has been reported for hepatitis B and hepatitis C viruses.

Although exclusive formula-feeding reduces the risk of mother-to-child transmission of HTLV-1, risk of malnutrition is a significant concern in developing countries, where malnutrition remains a significant contributor to infant mortality.

6.2 Prevention of Horizontal Transmission

HTLV-1 can also spread through contact with body fluids, whole blood or blood components. As ATLL is associated with prolonged infection acquired during vertical transmission, and with infection through blood transfusions, the purpose of the prevention of horizontal transmission is mainly to reduce the general pool of HTLV-1 carriers.

6.3 Transfusion and Sexual Transmission

HTLV-1 screening programs aimed at preventing transfusion-related transmission of HTLV-1 through systematic screening of all blood donors as a public health control measure have been implemented in many endemic areas, since 1986 (Inaba et al. 1989; Osame et al. 1990). Restricting breast-feeding and blood donor screening resulted in a decrease in HTLV-1 carriers from 2.79 to 0.44 % in Kagoshima Prefecture, southern Japan (Table 1). In HTLV-1 non-endemic areas, reports indicate that HTLV-1 infection may be concentrated in select donor populations, especially among immigrants from endemic areas. For developing countries, the cost of imported screening test kits may be prohibitive, necessitating the development of more cost-effective tools and programs for blood donor screening. In most African countries, transfusion remains a significant contributor to HTLV-1 transmission.

Table 1 Changes in the number of HTLV-1 carrier among blood transfusion donor at Kagoshima prefecture, southern part of Japan (1999–2008)

Year	The number of blood transfusion donor	The number of HTLV-1 carrier	%
1999	98,644	2,751	2.79
2000	91,456	1,368	1.50
2001	92,281	1,048	1.14
2002	89,458	827	0.92
2003	86,000	686	0.80
2004	82,310	565	0.69
2005	73,792	435	0.59
2006	69,133	388	0.56
2007	69,741	360	0.52
2008	71,226	313	0.44

Sexual transmission of HTLV-1 is primarily due to the transmission from men to women. Recommendations to prevent sexually transmitted infections should be emphasized, including condom use and avoiding multiple and anonymous sexual partners. Access to accurate information about HTLV-1 infection and appropriate counseling are important preventive strategies, as blood donor candidates and sexually active persons are usually asymptomatic and are primarily of reproductive age.

7 Development of Adult T-cell leukemia lymphoma

7.1 Pathogenesis of Adult T-Cell Leukemia/Lymphoma

The pathogenesis of ATLL is not completely understood. Extensive studies have revealed that HTLV-1 transactivator/transcriptional activator (Tax) plays a critical role in the transformation of virus-infected cells. Tax is thought to be a potent oncoprotein, as it results in immortalization of human primary T-cells and Tax transgenic mice malignancy. Tax enhances viral replication through transactivation of the viral promoter, the 5′ long tandem repeat (LTR), results in activation of the nuclear factor kappa-B (NF-kB) pathway, interferes with cell cycle regulators, induces aneuploidy and DNA damage, and impairs DNA repair. Thus, Tax is thought to play a key role in the pathogenesis of ATLL (Matsuoka and Jeang 2011).

HTLV-1 bZIP factor (HBZ) is coded for by the minus strand of the HTLV-1 provirus and can be found in all ATLL cells (Satou et al. 2006). HBZ protein was originally reported to suppress Tax-mediated viral transcription; however, HBZ RNA has also been shown to promote cell proliferation. Importantly, HBZ transgenic mice developed CD4/forkhead box protein-3 (Foxp3)-positive T-cell lymphoma, resembling the immunophenotype and clinical features of human ATLL. These findings suggest that HBZ is a critical factor in leukemogenesis. The proposed model for the interplay between Tax and HBZ is that Tax is needed to initiate the transformation of HTLV-1-infected cells, while HBZ is required to maintain the transformed phenotype in ATLL (Matsuoka and Jeang 2011).

7.2 Determinants of Progression from Asymptomatic Carrier Status to ATLL

The determinants of ATLL progression in HTLV-1 carriers have been investigated in many epidemiological and clinical studies. In Japanese cohorts, the average age at diagnosis is about 65 years (Yamada et al. 2011), significantly greater than in the Jamaican cohort, who present in their mid-forties, suggesting that other host and environmental factors may also be involved in ATLL pathogenesis (Hanchard 1996). The age at the time of HTLV-1 infection is also a critical factor in ATLL development, as ATLL rarely develops in HTLV-1 carriers who acquired infection

through horizontal transmission. Several studies have examined host genetic factors, including HLA haplotypes, due to the observation that patients with ATLL were more likely to have a family history of ATLL when compared with the general population. The frequency of HLA-A*26, HLA-B*4002, HLA-B*4006, and HLA-B*4801 alleles was significantly higher in ATLL patients than in HTLV-1 asymptomatic carriers in Japan (Yashiki et al. 2001). In the Miyazaki cohort, HTLV-1 carriers with a higher anti-HTLV-1 titer and lower anti-Tax reactivity were at greatest risk of developing ATLL (Hisada et al. 1998), and higher HTLV-1 proviral load was a significant risk factor for progression from asymptomatic HTLV-1 carrier status to ATLL. A nationwide prospective study of HTLV-1 carriers in Japan was initiated to identify the determinants of ATLL development. Fourteen subjects out of 1,218 asymptomatic carriers developed ATLL, and all of the 14 subjects had higher baseline proviral loads, whereas there were no cases of ATLL among those with a baseline proviral load of less than 4 copies/100 peripheral blood mononuclear cells (Iwanaga et al. 2010).

8 Prognosis for Patients with Adult T-Cell Leukemia/Lymphoma

8.1 Acute and Lymphoma Sub-Types

The prognosis for patients with acute and lymphoma subtypes of ATLL remains poor, even with chemotherapy or allogeneic hematopoietic stem cell transplantation (alloHSCT). With currently best available chemotherapy in one series (Tsukasaki et al. 2007), the rate of complete response (CR) was 40 % and overall survival (OS) at 3 years was 24 %. The median survival time (MST) is 13 months.

8.2 Chronic and Smoldering Sub-Types

In a previous study, in which Japanese patients with ATLL were followed for a total duration of 7 years, the 4-year survival rates for chronic and smoldering subtypes were 26.9 and 62.8 %, respectively, with a MST of 24.3 months for the chronic sub-type (Shimoyama 1991). Therefore, the chronic and smoldering subtypes of ATLL are characterized by an indolent clinical course and are usually managed by observation or "watchful waiting" until disease progression to acute crisis, which is similar to the approach to the management of chronic lymphoid leukemia or smoldering myeloma. However, a recent report with long-term follow-up of these indolent sub-types of ATLL (chronic and smoldering) revealed that the MST was 4.1 years and the estimated 5-, 10-, and 15-year survival rates were 47.2, 25.4, and 14.1 %, respectively (Takasaki et al. 2010), which were poorer than expected. These findings suggest that even patients with indolent forms of ATLL should be carefully observed in clinical practice, and further research is needed to improve the management of these patients.

9 Current Treatment Options

9.1 Conventional Chemotherapy

The results of a phase III randomized control trial suggest that the vincristine, cyclophosphamide, doxorubicin, and prednisone (VCAP); doxorubicin, ranimustine, and prednisone (AMP); and vindesine, etoposide, carboplatin, and prednisone (VECP) regimens show no benefit over biweekly cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) in newly diagnosed acute, lymphoma, or unfavorable chronic subtypes of ATLL in terms of OS, primary study endpoint, or progression-free survival (Tsukasaki et al. 2007). However, the rate of CR was higher in the VCAP-AMP-VECP arm than the biweekly CHOP arm (40 vs 25 %, respectively; $P = 0.020$). OS at 3 years was 24 % in the VCAP-AMP-VECP arm and 13 % in the CHOP arm ($P = 0.085$). Nonetheless, the MST of 13 months still compares unfavorably to other hematological malignancies.

9.2 Allogeneic Hematopoietic Stem Cell Transplantation

Allogeneic HSCT (alloHSCT) has been explored as a promising alternative therapeutic modality that can provide long-term remission in a proportion of patients with ATLL (Choi et al. 2011; Hishizawa et al. 2010; Utsunomiya et al. 2001). In a recent large nationwide retrospective analysis, investigators compared outcomes of 386 patients with ATL who underwent alloHSCT. After a median follow-up of 41 months, 3-year OS for the entire cohort was 33 % (Hishizawa et al. 2010). Another retrospective study based on 294 ATLL patients who received alloHSCT revealed that the development of mild-to-moderate acute GVHD confers a lower risk of disease progression and a beneficial influence on survival (Kanda et al. 2012), which is indicative of a graft-versus-ATLL effect. Another large retrospective analysis of alloHSCT for ATLL ($n = 586$) in Japan revealed no significant difference in OS between myeloablative conditioning (MAC) and reduced intensity conditioning (RIC). There was a tendency toward better OS in older patients receiving RIC (Ishida et al. 2012). The number of ATLL patients eligible for allogeneic transplantation is few because of older age at presentation and the low rate of CR. Selection criteria for alloHSCT for patients with ATLL remain to be determined.

9.3 Interferon-α (IFN-α) and Zidovudine (AZT)

Results of a recent meta-analysis on the use of AZT/IFN for 254 ATLL patients worldwide showed that the treatment of ATLL patients with AZT and IFN resulted in better response and prolonged OS (Bazarbachi et al. 2010). Two hundred and seven patients received AZT/IFN therapy. In these patients, 5-year OS rates were

46 % for 75 patients who received antiviral therapy ($P = 0.004$). In acute ATLL, achievement of complete remission with antiviral therapy resulted in 82 % 5-year survival. These results suggest that the treatment of ATLL using AZT/IFN results in high response and CR rates except for lymphoma type of ATLL, 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 conventional chemotherapy or alloHSCT are warranted.

9.4 Prevention of ATLL

The prevention of ATLL mostly relies on the prevention of HTLV-1 transmission as previously described. Another strategy could be the prevention of ATLL development among HTLV-1 carriers. Despite the prolonged carrier status before ATLL development, there are no interventions exploiting this window of opportunity to treat ATLL. This is partly because only approximately 10 % of HTLV-1 carriers develop HTLV-1-related disease in their lifetime. Careful risk–benefit analysis including the acceptability of side effects during interventions is needed.

9.5 Future Directions for the Prevention of ATLL

9.5.1 Immunological Impairment of HTLV-1-Specific T-Cells

Vertical transmission, high proviral loads, and suppression of HTLV-1-specific T-cell immune responses are important risk factors for ATLL development. It has been reported that Tax-specific cytotoxic T lymphocytes (CTLs) detected in chronic and smoldering ATLL and a subset of asymptomatic carriers are anergic to antigen stimulation (Takamori et al. 2011). Such functional impairment of CTLs seems specific to HTLV-1, as cytomegalovirus-specific CTLs, for example, remain intact.

In animal models, oral inoculation of HTLV-1 virions induces T-cell tolerance against HTLV-1 (Hasegawa et al. 2003). As breast-feeding is the main route of vertical transmission in HTLV-1 infection, this may induce neonatal T-cell tolerance against HTLV-1.

In addition to immunological tolerance, T-cell exhaustion may be another mechanism of antigen-specific T-cell suppression. We have reported on the upregulation of programmed death-1 (PD-1) expression on Tax-specific CTLs, suggesting Tax-specific T-cell exhaustion (Kozako et al. 2009).

9.5.2 Vaccine

Vaccination of uninfected individuals against HTLV-1 is not a sophisticated feasible strategy for the prevention of ATLL, as ATLL develops after a long latency period in individuals vertically transmitted HTLV-1 carriers within the first 6 months of life, and vertical transmission is almost completely prevented by

avoiding breast-feeding. Thus, the purpose of vaccination should be to augment HTLV-1-specific T-cell responses in asymptomatic carriers, enhancing clearance of infected and transformed cells, thereby protecting against ATLL.

HTLV-1 Tax-targeted vaccines in a rat model of HTLV-1-induced lymphomas showed promising antitumor effects (Ohashi et al. 2000). In addition, HTLV-1-immunized monkeys developed a strong cellular immune response with HTLV-1-derived peptide vaccines, and a significant reduction in HTLV-1 proviral load was observed in these immunized monkeys after challenge (Kazanji et al. 2006). Therefore, these results provide the scientific rationale for clinical use of such a vaccine for preventing ATLL. There remain, however, several obstacles to be overcome before clinical application can be realized. HTLV-1 synthetic peptides are poorly immunogenic, with inefficient induction of antigen-specific CTLs. We have shown in previous reports that oligomannose-coated liposomes (OMLs) encapsulating the HLA-A*0201-restricted HTLV-1 Tax-epitope (OML/Tax) resulted in the efficient induction of HTLV-1-specific T-cell responses (Kozako et al. 2011). Further, immunization of HLA-A*0201 transgenic mice with OML/Tax resulted in the efficient induction of HTLV-1-specific IFN-γ producing T-cells, and DCs exposed to OML/Tax showed increased expression of DC maturation markers. In addition, HTLV-1-Tax-specific CD8+ T-cells were efficiently induced by OML/Tax derived from HTLV-1 carriers ex vivo. OML/Tax increased the number of HTLV-1-specific CD8+ T-cells by an average 170-fold. Furthermore, these HTLV-1-specific CD8+ cells efficiently lysed HTLV-1 epitope peptide-pulsed T2-A2 cells. These results suggest that OML/Tax induces antigen-specific cellular immune responses without the need for adjuvants and may be an effective vaccine candidate to reduce progression to ATLL.

Better prognosticators would help identify individuals most at risk for progression to ATLL, allowing us to limit the exposure of lower-risk individuals to unwanted immunological responses to vaccination, including autoimmune-like conditions such as HAM/TSP.

10 Conclusion

To date, restricting breast-feeding by mothers with HTLV-1 infection has been the mainstay of HTLV-1 prevention thereby extending ATLL. Antenatal screening for HTLV-1 should be implemented in the endemic areas, with provision of accurate information and counseling. In addition, screening of blood donor candidates has been shown to be effective in preventing HTLV-1 transmission. Recommendations to prevent sexual transmission should be emphasized, including condom use and adopting safe sexual behavior. The development of an effective and safe vaccine could be an important tool in protecting HTLV-1-infected carriers against ATLL.

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