Chapter 6

Prevention of Human T-Cell Lymphotropic Virus Infection and Adult T-Cell Leukemia

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/55427

1. Introduction

1.1. Prevention of HTLV-1 and adult T cell leukemia/lymphoma (ATLL)

Human T-cell lymphotropic virus type 1 was first discovered as a human retrovirus that causes the T cell hematological malignancy, called adult T cell leukemia/lymphoma[1, 2]. The virus is transmitted through contact with bodily fluids containing HTLV-1 infected cells mostly from mother to child transmission through breastfeeding or blood transfusion. ATLL occur after prolonged incubation periods. Strategies for the prevention of ATLL should be divided into two steps. The first step is the prevention of HTLV-1 transmission. This has been established in some HTLV-1 endemic areas by screening for HTLV-1 among blood donors and refraining from breastfeeding among pregnant women who are HTLV-1 carriers. The second step is the prevention of ATLL development among HTLV-1 carriers. This has not been established at all. Approximately 90% of HTLV-1 carriers remain as healthy as uninfected individuals through their lifetime and the risk factors for developing ATLL remain to be defined. In addition, preventative intervention like vaccination may cause other unfavorable immunological consequences, thus well-examined strategies need to be further developed.

2. Epidemiology of HTLV-1 infection

1. Worldwide

Nearly 20 million people worldwide are estimated to be infected with HTLV-1[3]. Among them, only less than 10% develop HTLV-1 related disorders including adult T-cell leukemia/

lymphoma throughout their lives. A number of studies regarding the geographical and ethnoepidemiological distribution of the virus have been achieved in last 3 decades [4, 5], and revealed that southwestern Japan, tropical Africa, the Caribbean islands, and Central and South America are the endemic areas in the world. In Europe and North America, the prevalence is limited to the population emigrated from endemic areas.

2. Japan

The result of recent survey revealed that the estimated number of HTLV-1 carriers was at least 1.08 million in Japan[6]. 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

The route of infection has been shown to be related to the development of HTLV-1-associated diseases. ATLL has been mainly associated with breastfeeding and HTLV-1-associated myelopathy/tropical spastic paraparesis has been associated with blood transfusion[7]. ATLL cases of post-transfusion have been scarcely reported[8]. Three major routes of viral transmission have been established: [1] mother-to-child transmission, mainly via breast-feeding[9, 10]; sexual transmission, predominantly male to female[11, 12]; and [3] cellular blood compo-

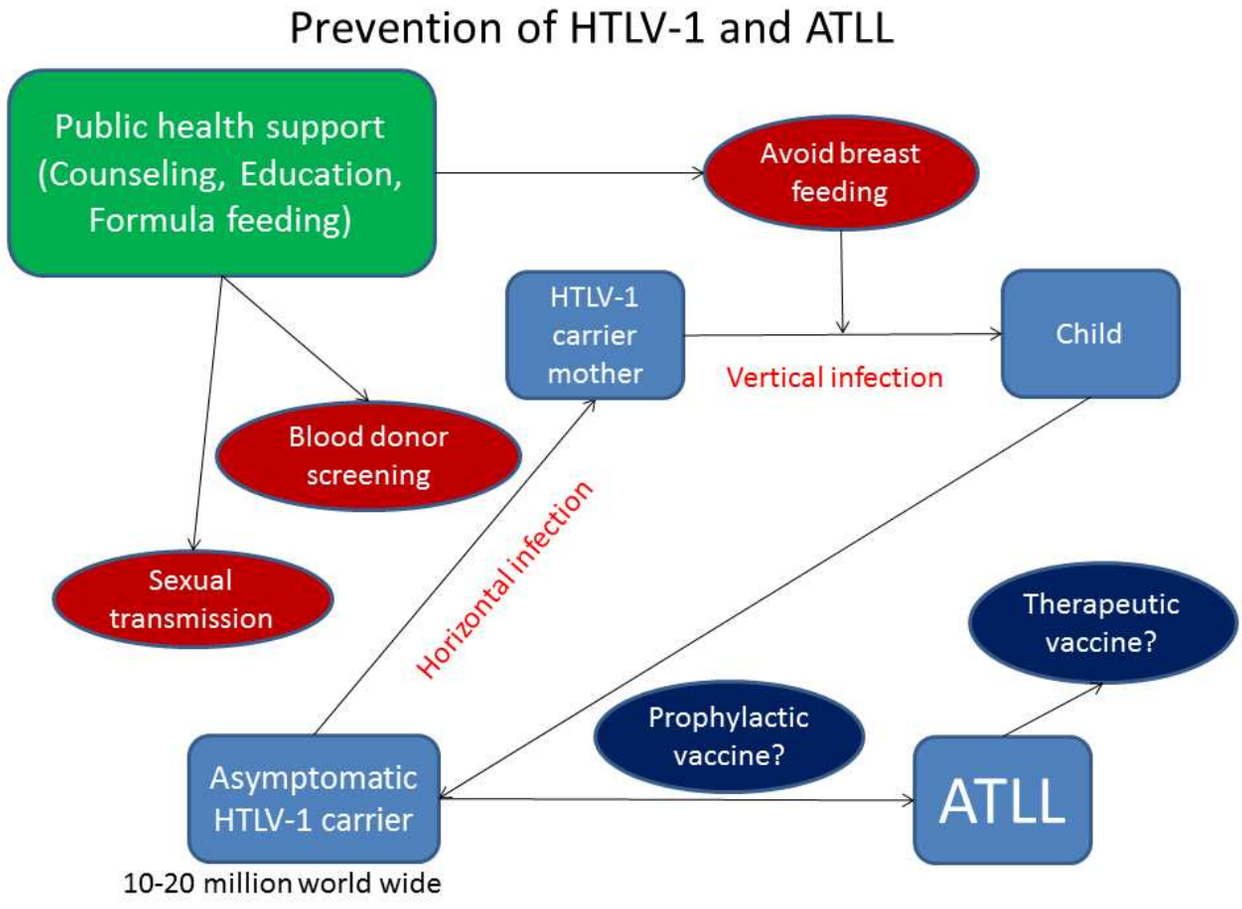

Figure 1. Prevention of HTLV-1 and ATLL

nents[13]. The efficiency of the mother-to-child transmission route is estimated to be around 20%[14]. Mother-to-child transmission during pregnancy or peripartum period has been reported to be less than 5%[15].

3. Epidemiology of adult T cell leukemia/lymphoma

Only a small proportion of HTLV-1 carrier develops ATLL after long latency period. Despite wide geographical distribution, the data regarding the incidence and prevalence of ATLL are scarce except for Japan. In addition the reported data might be underestimated for lymphoma type which resemble to other T cell lymphoma because of the difficulty of definite diagnosis in less developed countries. Among Japanese population, the incidence of ATLL among carriers is estimated to be 4.5-7.3% in men and 2.6-3.5% in women [16-18]. ATLL is reported to develop among individuals predominantly in their fifth decade in Japan [19], in the Jamaican and Brazilian series, patients tend to present the disease in the fourth decade, which suggest other immunological background or local factors may play a role in the disease development[20, 21].

4. Mechanisms of HTLV-1 transmission

HTLV-1 can infect a wide variety of human cell types in vitro [22, 23], thus its receptor is thought to be a ubiquitously expressed molecule. GLUT1, heparin sulfate proteoglycan(HSPG) and neuropilin-1 are the three molecules that are reported as key players for the interaction between the viral envelop and the cell membrane, and for the entry into the cells [24-26]. It has been proposed that HTLV-1 particles first contact HSPG, then neuropilin-1 recruits HTLV-1/HSPG complex to present them to GLUT1. HSPG/neuropilin-1/GLUT1 complex makes the viral envelop competent for membrane fusion and entry into the cell.

Cell-free HTLV-1 virions are poorly infectious in vitro for most of cell types including their primary target cells, CD4 T cells. The main transmission pattern of HTLV-1 is cell-to-cell contact, however, only myeloid and plasmacytoid dendritic cells can be infected by cell-free HTLV-1[27]. This route may be important in the setting of mother-to-child transmission through breast-feeding. Dendritic cells may play an important role during initial acquisition of infection, milk-to-mucosal transmission of the virus.

Three major mechanisms of cell-to-cell transmission of HTLV-1 have been proposed: [1] HTLV-1-infected lymphocytes polarized their microtubules and viral components upon contact with other T cells, forming so-called virological synapses[28]; [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, which resemble bacterial biofilms. Extracellular viral assemblies rapidly adhere to other cells upon cell contact, allowing virus spread and infection of target cells[29]; and [3] 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[30].

5. Prevention of transmission of HTLV-1

The prognosis for ATLL is one of the worst among hematological malignancies with best available therapy, and no preventative vaccine against HTLV-1 is yet available. Thus the prevention of transmission of HTLV-1 is the most realistic way to prevent the progression of ATLL.

5.1. Prevention of vertical transmission

Retrospective and prospective epidemiological studies revealed the mother-to-child transmission rate was around 20%[14]. Prevention of mother-to-child transmission has the most significant impact on the occurrence of HTLV-1 infection and associated diseases. Avoidance of breastfeeding is of the essence as it is the major form of vertical transmission of this virus. A prefecture-wide intervention study in Nagasaki Prefecture in Southern Japan to refrain from breast-feeding by carrier mothers revealed a marked reduction of HTLV-1 mother-to-child transmission from 20.3% to 2.5%. Thus, prenatal screening for HTLV-1 should be employed in endemic areas, combined with relevant counseling of carrier mothers regarding transmission of HTLV-1 through breastfeeding. Although children breast-fed for less than 6 months has significantly lower incidence of HTLV-1 infection than those breast-fed for more than 6 months, their chances of infection are significantly higher than those of bottle-fed children. Thus exclusive bottle-feeding is recommended[31].

Even with exclusive bottle-feeding, 2.5% of infants born to carrier mothers were infected with HTLV-1. As intrauterine transmission of HTLV-1 should be rare, transplacental transmission during delivery is most likely as is the case for other viruses, i.e. HBV and HCV.

Even though the dramatic impact of bottle feeding on mother-to-child transmission of HTLV-1, public health policies should consider the risk of malnutrition, especially in developing countries where the malnutrition is the primary causes of infant deaths. An alternative feeding formula should be recommended for children at risk of acquiring HTLV-1 infection through mother's milk. The practice of cross-feeding should also be avoided.

5.2. Prevention of horizontal transmission

HTLV-1 can also be spread through contact with bodily fluids such as whole blood or whole blood products. The development of ATLL related to transfusion is exceptional. Thus, the purpose of prevention of horizontal transmission is mainly to reduce HTLV-1 carrier population.

5.3. Transfusion and sexual transmission

HTLV-1 screening program to prevent transfusion-related transmission of HTLV-1 has been developed since 1986 and many countries in endemic areas started to employ systematic screening

http://dx.doi.org/10.5772/55427

of all blood donors [7, 32]. Screening of blood donor candidates has been shown to be an effective strategy in preventing HTLV-1 transmission. For HTLV-1 non-endemic areas, reports showed that the risk of HTLV-1 infection might be enhanced in some selected donor populations, especially in immigrants from endemic area, recommending the employment of policies for selective donor recruitment. For developing countries, the high cost of imported screening test kit is not negligible, thus, more cost effective strategies for blood donor screening need to be developed. In most African countries, transfusion still represents a risk of HTLV-1 transmission.

Most of sexual transmission of HTLV-1 is from men to women. Recommendations to prevent sexually transmitted infections should be emphasized, including condom use and avoiding multiple and unknown sexual partners. Nonetheless, access to correct information about HTLV-1 infection and appropriate counseling is very important as blood donor candidates and sexually active people are usually asymptomatic and in reproductive age.

6. Pathogenesis of adult T cell leukemia/lymphoma

The pathogenesis of ATLL is not completely understood. Extensive studies have revealed that HTLV-1 transacting transcriptional activator (Tax) plays a critical role in the transformation of virus infected cells. Tax is thought to be a potent oncoprotein, as it solely immortalizes human primary T cells and Tax transgenic mice develop spontaneous tumors. Tax enhances viral replication through transactivation of the viral promoter, the 5'LTR, and its multifaceted functions including activation of NF-kB pathway, cell cycle progression, induction of aneuploidy, induction of DNA damage and impairment of DNA repair. Thus, Tax is thought to play a key role in the pathogenesis of ATLL[33].

HTLV-1 bZIP factor (HBZ) is encoded in the minus strand of the HTLV-1 provirus, and is ubiquitously expressed in all ATLL cells [34]. HBZ protein was originally reported to suppress Tax-mediated viral transcription, however, HBZ RNA possesses cell proliferation function. Importantly, HBZ transgenic mice developed CD4/Foxp3 positive T-cell lymphoma, which resembles the phenotype of human ATLL. These findings suggest that HBZ is a critical factor in leukemogenesis. Possible hypothesis of the interplay between Tax and HBZ is that Tax is needed to initiate transformation of HTLV-1 infected cells while HBZ is required to maintain the transformed phenotype in ATLL[33].

7. Determinants for ATLL progression inHTLV-1 carriers

The determinants for ATLL progression in HTLV-1 carriers have been investigated in many epidemiological and clinical studies. ATLL is named after its adult onset time of the disease, thus age is the most well-known factor. The recent survey from Japan reported that the age at diagnosis was around 65 years [35]. However the average age at diagnosis of ATLL in Jamaica was mid-forties[36], thus other host factors and environmental characteristics may also affect the disease onset. The age at time of HTLV-1 infection is also a critical factor for ATLL development as ATLL

scarcely develops in HTLV-1 carriers by horizontal infection. Early studies suggested that patients with ATLL had more family history of ATLL than that in the general population, thus several host genetic background factors have been investigated including HLA haplotype. The frequency of HLA-A26, HLA-B4002, HLA-B4006 and HLA-B4801 alleles were significantly higher in ATLL patients than in HTLV-1 asymptomatic carriers in Japan [37]. Several laboratory markers were investigated for ATLL development. A series of Miyazaki cohort study reported that HTLV-I carriers with a higher anti-HTLV-I titer and a lower anti-Tax reactivity may be at greatest risk of ATLL [38]. The Miyazaki study also reported that the levels of HTLV-1 proviral load was higher in HTLV-1 carrier who developed ATLL than in asymptomatic HTLV-1 carriers. A nationwide prospective study for HTLV-1 carrier was initiated to investigate the determinant of ATLL development. 14 subjects out of 1218 asymptomatic carrier developed ATLL and all of the 14 subjects had higher baseline proviral load. None developed ATLL among those with a baseline proviral load less than 4 copies/100 peripheral blood mononuclear cells [39].

8. Prognosis of adult T cell leukemia/lymphoma

1. Acute type and lymphoma type

The prognosis of acute type and lymphoma type of ATLL remain poor with chemotherapy or allogeneic hematopoietic stem cell transplantation. With currently best available chemotherapy [40], the rate of complete response was 40%. Overall survival at 3 years was 24%. The median survival time is 13 months.

2. Chronic type and smoldering type (indolent type ATLL)

A previous study, in which Japanese patients with ATLL were followed for a maximum duration of 7 years, reported that the 4-year survival rates for chronic, and smoldering type were 26.9%, and 62.8% respectively, with the median survival time (MST) of 24.3 months, and not yet reached, respectively[41].Therefore, the chronic and smoldering subtypes of ATLL are considered indolent and are usually managed with watchful waiting until disease progression to acute crisis, similar to the management of chronic lymphoid leukemia or smoldering myeloma. However, recent report with long term follow-up of indolent ATLL (chronic and smoldering type) revealed that the median survival time was 4.1 years and the estimated 5-, 10-, 15-year survival rates were 47.2%, 25.4% and 14.1%, respectively[42]. The prognosis of indolent ATLL in this study was poorer than expected. These findings suggest that even patients with indolent ATLL should be carefully observed in clinical practice.

9. Current treatment option

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

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(AMP); and vindesine, etoposide, carboplatin, and prednisone (VECP) regimen is not superior to biweekly cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) in newly diagnosed acute, lymphoma, or unfavorable chronic types of ATLL in terms of overall survival(OS), which is primary endpoint of this study, or progression free survival [40].However, the rate of complete response (CR) was higher in the VCAP-AMP-VECP arm than the biweekly CHOP arm [40% *v* 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 median survival time of 13 months still compares unfavorably to other hematologic malignancies.

9.2. Allogeneic hematopoietic stem cell transplantation (alloHSCT)

alloHSCT has been explored as promising alternative therapeutic modality that can provide long-term remission in a proportion of patients with ATLL[43-45]. In a recent large nationwide retrospective analysis, investigators compared outcomes of 386 patients with ATL who underwent allogeneic HSCT. After a median follow-up of 41 months, 3-year overall survival for entire cohort was 33% [45]. Retrospective analysis 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 [46], which is the indicative of the presence of a graft-versus-ATLL effect. Another large retrospective analysis of alloHSCT for ATLL (n=586) in Japan revealed that no significant difference in OS between myeloablative conditioning (MAC) and reduced intensity conditioning (RIC) regimen was observed. There was a trend indicating that RIC contributed to better OS in older patients[47]. The number of ATLL patients eligible for allogeneic transplantation is quite limited because of older age at presentation and the low rate of CR. Selection criteria of alloHSCT for patients with ATLL remain to be determined.

9.3. Interferon-α (IFN-α) and zidovudine (AZT)

The results of a recent worldwide meta-analysis on the use of AZT/IFN for 254 ATLL patients, the treatment of ATLL patients with AZT and IFN resulted in better response and prolonged overall survival[48]. Two hundred seven patients received first-line AZT/IFN therapy. In these patients, five-year overall survival rates were 46% for 75 patients who received first-line 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 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.

10. Prevention of ATLL

The prevention of ATLL mostly relies on the prevention of HTLV-1 transmission as previously described. Another way is the prevention of ATLL development among HTLV-1 carriers. Even

though long-term opportunity to intervene the HTLV-1 carrier status, this has not been achieved at all at any stages. This is partly because only approximately 10% of HTLV-1 carriers develop HTLV-1 related disease in their lifetime. Risk-benefit balance including acceptable side effect during intervention are needed to be carefully assessed.

11. Future direction of prevention of ATLL development

11.1. Immunological impairment of HTLV-1 specific T cells

Vertical transmission, high proviral loads, and suppression of HTLV-1-specific T-cell immune responses are reported to be associated with risk factors for ATLL development. It has been reported that Tax specific cytotoxic T lymphocytes (CTLs) detected in chronic and smoldering ATLL and subset of asymptomatic carriers are anergic to antigen stimulation [49]. Such functional impairment of CTLs seems specific to HTLV-1 as cytomegalovirus-specific CTLs remain intact.

In animal models, oral inoculation of HTLV-1 virions induces T cell tolerance against HTLV-1[50]. 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 PD-1 expression on Tax-specific CTLs may indicate Tax-specific T cell exhaustion [51].

12. Vaccine

Vaccination of HTLV-1 against uninfected individuals is not sophisticated strategy for prevention of ATLL as most of ATLL develop after long incubation period among vertically transmitted HTLV-1 carriers within 6 months of their lives and vertical transmissions are almost completely prevented by refraining breastfeeding. Thus, the purpose of vaccination is to augment HTLV-1-specific T-cell response to reduce the risk of development of ATLL in such above mentioned subpopulation.

i. HTLV-1 Tax-targeted vaccines in a rat model of HTLV-1-induced lymphomas showed promising antitumor effects [52]. In addition, the HTLV-1-immunized monkeys developed a strong cellular immune response with HTLV-1 specific-peptides and a significant reduction in the proviral load was observed in these immunized monkeys after challenge [53]. Therefore, these results provide a rationale for clinical use of such a vaccine for preventing ATLL. However, there are several obstacles to overcome for clinical use. One major obstacle is that HTLV-1 specific synthetic peptides are poorly immunogenic to elicit efficient induction of antigen-specific CTLs. We have explored the efficient induction of HTLV-1-specific T cell responses by oligomannose-coated liposomes (OMLs) encapsulating the HLA-

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A*0201-restricted HTLV-1 Tax-epitope (OML/Tax)[54]. Immunization of HLA-A*0201 transgenic mice with OML/Tax resulted in the efficient induction of HTLV-1-specific IFN-γ producing T cells. Dendritic cells (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. OML/Tax increased the number of HTLV-1-specific CD8+ T cells by average 170-fold, while treatment without antigen showed an increase of 9-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 carrier to augment HTLV-1-specific T-cell response to reduce the risk of development of ATLL.

ii. Nonetheless, for the clinical use of HTLV-1 vaccine, extraction of high risk group for ATLL needs to be clearly defined to avoid unwanted immunological consequence including other HTLV-1 associated inflammatory diseases.

13. Conclusion

So far, the prevention of ATLL totally relies on the prevention of vertical HTLV-1 transmission by refraining breastfeeding from HTLV-1 carrier mother. Prenatal screening of HTLV-1 should be implemented in the endemic area with careful 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 should be emphasized.

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