ISSN: 2230-9926

Available online at http://www.journalijdr.com

IJDR

International Journal of Development Research
Vol. 09, Issue, 12, pp. 32578-32583, December, 2019

RESEARCH ARTICLE OPEN ACCESS

ADULT T-CELL LEUKEMIA/ LYMPHOMA: FROM EPIDEMIOLOGY TO TREATMENT

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ARTICLE INFO

Article History:
Received 07th September, 2019
Received in revised form
19th October, 2019
Accepted 28th November, 2019
Published online 31th December, 2019

Key Words:
Adult T cell leukemia lymphoma;
HTLV1; ATL.

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ABSTRACT

Adult T-cell leukemia/lymphoma is a lymphoproliferative disorder of mature T cells caused by humain T-cell lymphotropic virus1, the clinical features of the disease can vary greatly. Patients with adult T-cell leukemia/lymphoma have a poor prognosis because of cell resistance to conventional intensive chemotherapy and severe immunosuppression. The combination of Zidovudine and Interferon- is highly effective in the leukemic subtypes and should be considered as standard first-line therapy in that setting. Adult T-cell leukemia/lymphoma patients still benefit from chemotherapy induction with concurrent or sequential antiretroviral therapy with Zidovudine / Interferon.

Citation: Bouanani, N. and Lamchahab, M. 2019. "Adult t-cell leukemia/ lymphoma: from epidemiology to treatment", *International Journal of Development Research*, 09, (12), 32578-32583.

INTRODUCTION

Adult T-cell leukemia / lymphoma (ATL) is a tumor proliferation of activated mature T lymphoid cells, the etiological agent of which is the HTLV1 human retrovirus (human T cell-leukemia virus type 1) [1], the areas of high endemicity of the virus are southern Japan and intertropical Africa (Bazarbachi *et al*., 2011; Gessain, 2012). Tax viral oncoprotein is a major player behind ATL, which acts by interfering with apoptosis, cell proliferation and repair of deoxyribonucleic acid (DNA) (Bazarbachi, 2011). Four anatomoclinical forms are described (Pasquier, 2004). The prognosis remains very severe, whatever the clinical form, because of the resistance of the cells to anti-tumor chemotherapy and deep immunodepression (Gessain, 2011). Observation without treatment or Watchful waiting, antiviral therapy, chemotherapy followed by allograft and targeted therapy are all therapeutic options adapted to different clinical forms (Tsukasaki, 2014).

Epidemiology

Infection with the HTLV-1 virus (human T leukemia virus 1) affects between 15 and 25 million people worldwide, the highly endemic areas are southern Japan (1.1 million), Africa intertropical, the Caribbean Basin in Central and South America, parts of the Middle East and Melanesia. The prevalence is about 150 times higher in the French West Indies (1 to 2% of the general population) than in metropolitan France (Tsukasaki, 2014 and Gessain, 2012). There are localized foci of very high endemicity such as the Kyushu and Okinawa Islands (up to 30% of the population), some parts of Gabon or Guyana and some Indian populations in northwestern Argentina. In endemic areas, 700 new cases are identified each year with an average prevalence of 2% to 5% among carriers of the virus (Gessain, 2011 and Besuschio, 2003). ATL affects adults with peak incidence between 50-69 years, mostly men (1.4 / 1) (Pasquier, 2004). Viral transmission occurs, on the one hand, from mother to child, mainly through prolonged breastfeeding for more than six months. The risk factors associated with this mode of transmission are, in addition to prolonged breastfeeding, a high anti-HTLV-1 antibody titer in the mother as well as a high HTLV-1 proviral load in the blood and breast milk. On the other hand, this virus is transmitted by sexual contact, with a preferential, but not exclusive, transmission in the man - woman sense. HTLV-1 is also transmitted by blood during transfusion of blood products containing infected T cells, the transmission rate by transfusion is high in the recipient, of the

order of 10-50% for a transfusion containing cells. infected with infection (Gessain, 2011).

Pathophysiology

HTLV-1 (Human T cell leukemia / lymphoma virus type 1), an exogenous retrovirus discovered in humans, isolated in the United States, in R. Gallo's laboratory from a culture in 1980 of CD4 + T cells. These cells came from the peripheral blood of a patient with T haematodermia, initially considered to be cutaneous T lymphoma with a leukemic phase (Gessain, 2011). ATL is a proliferation of activated mature CD4 + T cells carrying CD4 and CD25 markers (Fukuoka, 2013). These cells are characterized by monoclonal integration of the HTLV-1 provirus into the lymphocyte genome. Incubation is very long (up to 60 years). ATL would occur when, following alterations in the host genome, clones of infected CD4 + T cells are no longer controlled by the T immune response (Pasquier, 2004). There are several subtypes of the HTLV1 virus whose distribution differs according to the geographical origin of the patient. To date, seven viral HTLV1 genotypes have been described, including four major ones (A, B, C, D) (Gessain, 2011). In addition to the gag, pro, pol, and env genes common to all retroviruses, the HTLV1 genome has open reading frames encoding regulatory and helper proteins including tax proteins and HBZ (Mahieux, 2011). Risk factors for ATL development in an infected person include early life-stage infection, advanced age, male sex, family history of ATL, and high proviral load. It is probably a multi-stage carcinogenesis, so it is possible to distinguish schematically three large successive steps (Figure 1).

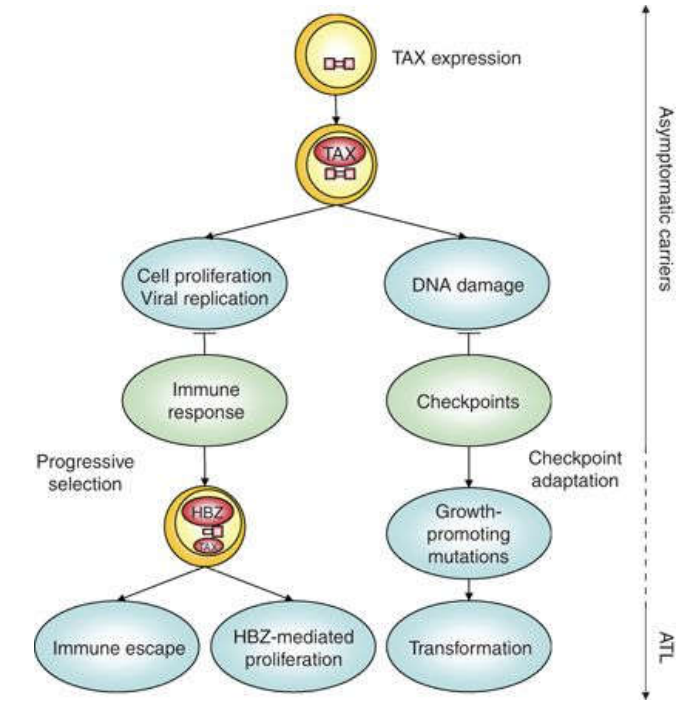

Figure 1. Mechanisms of HTLV-1 persistence and transformation [5,7]

The first corresponds to primary infection with HTLV-1 during prolonged breastfeeding. Almost all (> 95%) of ATLs occur in patients who have been infected with this pathway. The second step is the clonal expansion of infected T cells that appears to be significantly related to the protein Tax (regulatory protein). The early expression of the transactivating protein Tax causes, through the activation of the signaling pathways, the deregulation of the mechanisms of control of cell proliferation, thymocyte maturation, apoptosis and DNA repair. participates in the immortalization of T cells. The exact role of cofactors, such as infection with S. stercoralis, is still poorly understood (Gessain, 2011; Mahieux, 2011 and Césaire, 2003). The third phase corresponds to the acquisition of genetic alterations of the host cell. Regression of Tax expression allows escape to tumor immunosurveillance while HBZ protein is expressed continuously. The role of the HBZ protein appears important for tumor proliferation, especially in late stages of the disease (Gessain, 2011), (Figure 2).

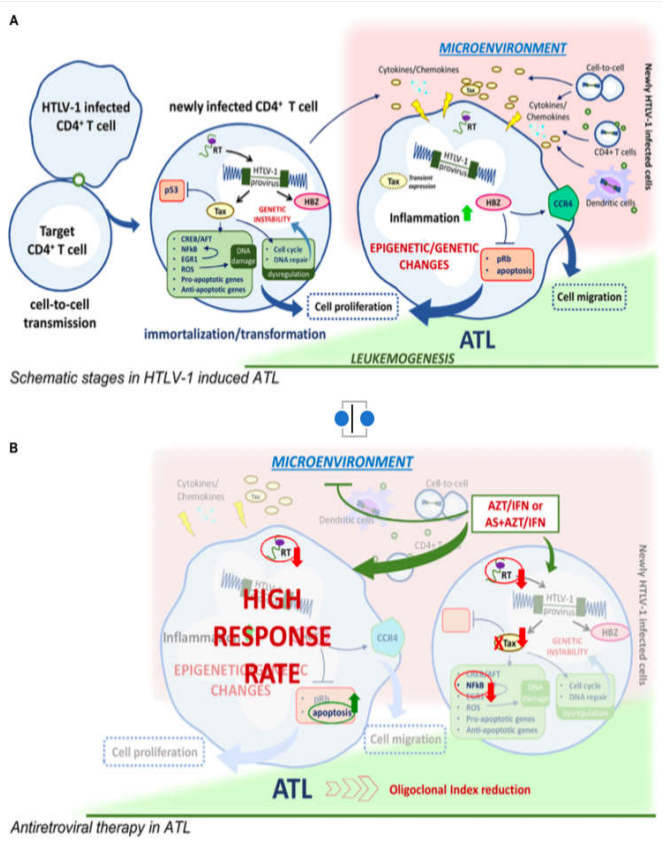

Figure 2. Schematic stages in HTLV1 –induced ATL [5,7]

Infection with HTLV1 can lead to chronic neuromyelopathy, initially known as tropical spastic paraparesis (TSP) and then HTLV-1 associated myelopathy (HAM), this chronic myelopathy is currently called TSP / HAM (Primo, 2009). HTLV-1 is also associated with rare infectious dermatitis that has been mainly diagnosed in young children in Jamaica, Brazil and Africa, anterior uveitis, rare cases of polymyositis or inclusion myositis, Lymphocytic alveolitis and lymphoid interstitial pneumonias, cases of chronic polyarthritis (Gessain, 2011; Primo, 2009 and Fukuoka, 2013).

Clinical Presentation: ATL is a peripheral T-cell lymphoma that occurs several decades after the initial infection on average 40 to 60 years. The clinical presentation associates voluminous polyadenopathies, hepatosplenomegaly, skin lesions, lytic bone lesions, frequent diffuse and interstitial medullary involvement, hypercalcemia, elevated lactic dehydrogenases (LDH), renal insufficiency and, inconsistently, neurological, gastrointestinal manifestations. in the lungs, T-immunodepression is often associated with opportunistic infections (Bazarbachi, 2011).

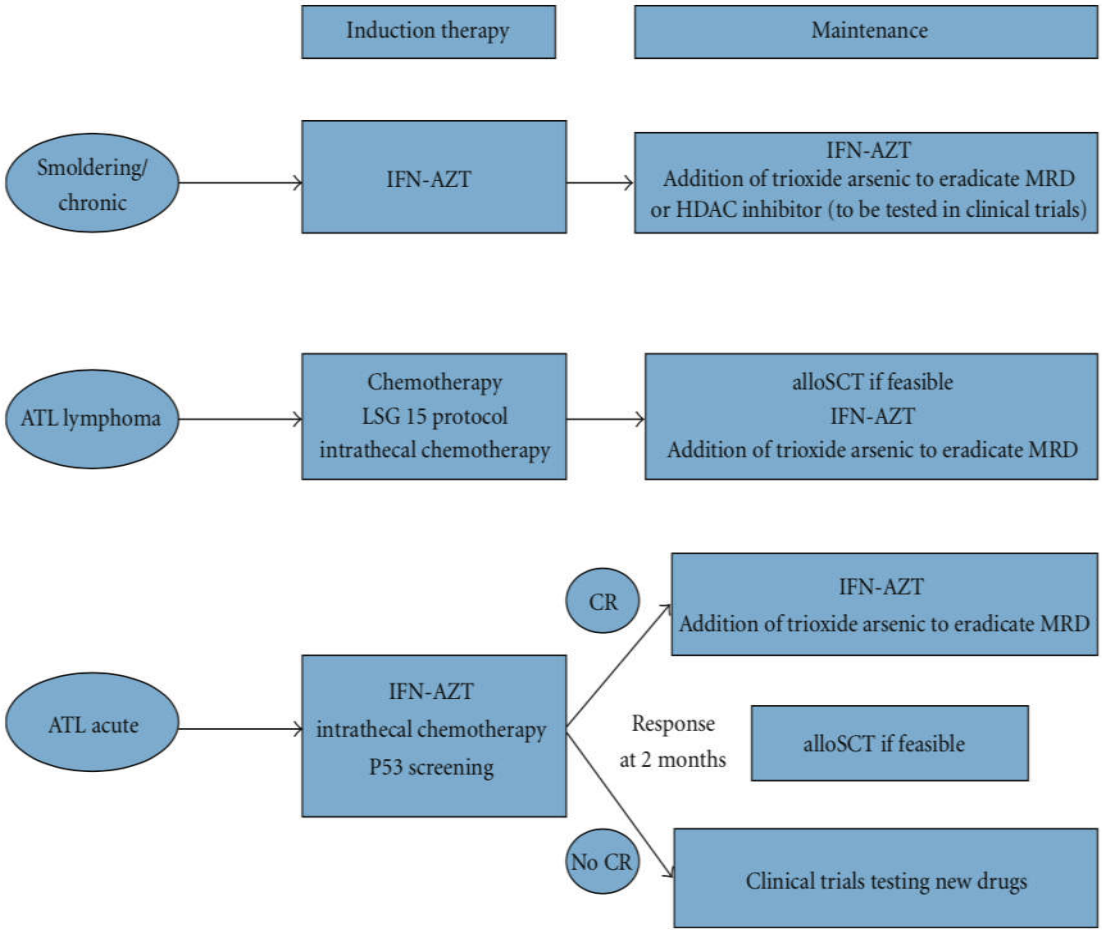

Figure 3. Recommended treatment strategy for patients with acute, lymphoma, or chronic/smoldering ATL (CR: complete remission; MRD: minimal residual disease; AZT: zidovudine; IFN: interferon-alpha; alloSCT: allogeneic stem cell transplantation) [21]

Paraclinic

1- Peripheral blood: The incidence of anemia and thrombocytopenia is variable, hyperleucocytosis with hyperlymphocytosis is seen in acute forms, eosinophilia is common (Tsukasaki, 2009 and Matutes, 2007).

2- Blood smear: The diagnosis of ATL is based on the demonstration on the peripheral blood of the patients of the cells with a homogeneous polylobed nucleus and condensed chromatin, small or absent nucleolus, agranular basophilic cytoplasm, these cells are called flower cells and are pathognomonic ATL. In some cases these pathognomonic ATL cells are not found and immunolabeling and HTLV1 serology have been used to make the diagnosis [11,12].

3- Immunophenotype: ATL cells have a mature CD4 + T cell phenotype and express CD2 + CD5 + CD25 + CD29 +, CD45RO +, alpha beta receptors of T cells, HLADR +, CCR4 + (chemokine receptor 4), Fox P3 + with CD7 negativity, CD8 and CD26 and reduction of CD3 expression. The majority of ATL cells are CD52 positive. The important expression of Ki 67 has an unfavorable prognostic significance. The minimal panel for the diagnosis of ATL includes CD3, CD4, CD7, CD8 and CD25 (Tsukasaki, 2014; Tsukasaki, 2009 and Matutes, 2007).

4- Biopsy: The biopsy is indicated when the diagnosis of the ATL is not obtained from the peripheral blood or when there is appearance of new lesions in the indolent form treated by abstention and surveillance, the biopsy can be done in different sites at the level ganglion, spleen, lung, gastrointestinal tract or other (Tsukasaki, 2009 and Matutes, 2007).

5- Cytogenetics: The cytogenetic study by conventional cytogenetics or fluorescent in situ hybridization (FISH) shows nonspecific abnormalities, more complex in the aggressive form compared to the indolent form (Tsukasaki, 2009 and Matutes, 2007).

6- Molecular biology: The mutation or deletion of the tumor suppressor genes p53, p15, p16 is observed in half of the ATL patients, the expression of IRF4 is predictive of the response to treatment (Tsukasaki, 2009 and Matutes, 2007).

7- Diagnosis of HTLV1 infection: The biological diagnosis of an HTLV-1 infection is based on a screening step: the detection of antibodies by immunoenzymatic tests (ELISA technique). However, the evidence of the causal link between the tumor and HTLV-1 is only brought to the formal level by demonstrating the clonal integration of the virus into the tumor cells. This clonal integration can be demonstrated by Southern blot in leukemic, ganglionic or cutaneous infiltrate cells. However, it is a rarely performed examination because it is long, expensive, insensitive, requires a lot of tumor material and is performed only in a few specialized laboratories. A particular amplification technique or Reverse Polymerase Chain reaction (Inverse PCR) can also be used to demonstrate the clonal integration of HTLV-1 into the currently most used tumor cells technique. It is therefore easy to understand that the diagnosis of ATL is difficult in many HTLV-1 endemic areas, particularly in Africa,

where this diagnosis is rarely made (Pasquier, 2004; Gessain, 2011 and Valensie, 2004).

8-Tumor marker: The soluble form of the interleukin-2 receptor alpha is a high tumor marker in aggressive, indolent and HTLV1 infection compared to normal subjects, detects early relapse and transformation of indolent forms. Thymidine kinase is a promising new tumor marker, but in practice in ATL, the main marker that reflects the tumor mass is LDH (Tsukasaki, 2009).

9- Bone marrow biopsy: Not necessary to make the diagnosis, but the marrow infiltration has a prognostic value (Tsukasaki, 2009).

10- Radiologic imaging and endoscopy: The C scan of the neck, thorax, abdomen and pelvis are mandatory to detect sites of nodal and extranodal ATL disease. The exploration of the central nervous system is based on brain imaging and lumbar puncture, that of the digestive tract on digestive endoscopy and biopsy.

In literature we found high rates of FDG positivity in T-cell lymphoma, and we recommend that patients with T-cell lymphoma be scanned from vertex to feet by use of PET/CT.

Differential diagnosis: Arises primarily with other T-cell lymphoma including fungoid mycosis, Sézary syndrome, some rare forms of Hodgkin lymphoma and angio-immunoblastic lymphoma, patients with latent forms can be confused with asymptomatic carriers of HTLV1 (Matutes, 2007).

Clinical forms: The classification of Shimoyama (1991) describes four clinical forms: acute, lymphomatous, chronic and latent form known as "smoldering" (Bazarbachi, 2011). The most frequent aggressive forms are the acute and lymphomatous forms (60% and 20% respectively) of all ATLs, the distinction between the two forms is based on the circulating abnormal lymphocyte level < 1% for the lymphomatous form and > 1% for the acute form. The indolent forms include chronic and latent forms, latent forms are accompanied by cutaneous or pulmonary infiltration without other associated visceral involvement, a normal level of white blood cells and 1 to 5% of abnormal lymphocytes on the peripheral blood whereas the forms chronic are accompanied by tumor syndrome made of lymphadenopathy and hepatosplenomegaly with elevated white blood cell count and they are classified into favorable and unfavorable groups, the latter are defined by the existence of hypoalbuminemia, increase of LDH or the urea and strong expression of Ki 67. Indolent forms are not accompanied by hypercalcemia or infiltration of the central nervous system or gastro-intestinal or bone disorders or significant elevation of LDH < 2 times the normal limit, these forms can evolve into aggressive forms in about 25% of cases, often after a period of 2 to 3 years (Bazarbachi, 2011).

Complications: The complications are mainly infectious represented by opportunistic infections related to immunosuppression mainly related to HTLV-1-induced cellular immunity, including in "healthy carriers". HTLV-1 / Anguillulosis or Strongyloides stercoralis co-infection leads to severe forms and resistance to anthelmintic treatments. As a result, screening and treatment of anguillulosis in ATL patients is systematic. Pneumocystis carinii pneumonia is an opportunistic infection that is also observed and requires systematic prevention. Toxoplasmosis, cryptococcosis, cytomegalovirus, bacterial abscess and fungal infections are also described (Boury, 2012; Montes, 2009 and Stewart, 2011).

Prognosis: The prognosis is very variable depending on the form but generally poor compared to other peripheral T lymphomas: a few months in the acute form, 1 to 5 years in the chronic form, 1 to 2 years in the lymphomatous form and up to 10 years in the form of slow evolution. The main prognostic factors that constitute a risk model have been reported in a series including 854 patients: the elevation of lactic dehydrogenases (LDH), an alteration of the performance index, an age greater than 40 years, a high number of sites. with hepatic impairment and hypercalcemia (Tsukasaki, 2009). Other factors are added, associated with an unfavorable prognosis: thrombocytopenia, eosinophilia, the increase of the beta 2 microglobulin, the hypoalbuminemia, the elevation of the serum urea level, the medullary involvement, the elevation of serum interleukin-5, serum CD25, expression of C-C chemokine receptors, proliferation index: Ki 67, p53 mutation and deletion p16 (Tsukasaki, 2009; Katsuya, 2012; Tobinai, 2004). The prognostic index of ATL is a promising new tool ranking patients in low, intermediate and high risk and is calculated according to 5 parameters: age, performance index, stage, serum albumin and soluble receptor for interleukin-2 (Katsuya, 2012).

Traitement

Preventive treatment: consists of two components, the first is the prevention of HTLV1 infection by prohibiting the breastfeeding of children born to HTLV-1 infected mothers, the use of condoms, and screening in blood donors. While condom use is feasible, screening of blood donors and the prohibition of breastfeeding in countries such as Japan are more difficult to apply in African countries where endemicity is often lower and limited. The second is the prevention of ATL development among HTLV-1 + patients. This has not been established in part because approximately 2 to 5% of HTLV-1 carriers develop the disease. As a result, several studies are being evaluated to study the predisposing factors for the development of ATL (Pasquier, 2004 and Gessain, 2011).

Curative treatment: Treatment of ATL remains very disappointing because of the chemoresistance and severe immunosuppression, the use of the usual polychemotherapy of non-Hodgkin's lymphoma or lymphoid leukemias results in little remission. Thus, in the leukaemic and lymphomatous forms, multidrug therapy does not make it possible to obtain more than 10% survival at four years, and the median survival rate is of the order of six months (Gessain, 2011). The treatment of ATL differs according to the clinical form, the different therapeutic strategies are summarized in Figure 3. For acute forms, combinations of chemotherapy have failed to have a significant impact on survival, the authors initially advocate screening for the P53 mutation that leads to resistance to the combination Zidovudine (AZT) / interferon-alpha (IFN), induction therapy with AZT and interferon alpha with neuro-meningeal prophylaxis based on intrathecal chemotherapy, for patients in complete remission (CR) AZT / IFN maintenance treatment is initiated, for those who would not not obtained a CR, they are included in clinical trials testing new molecules, the allograft is the preferred option for young subjects with donor (Marçais, 2012 and Nasr, 2014).

Treatment of the lymphomatous form is based on induction chemotherapy LSG15 (lymphoma study group) which is the combination of 6 cycles of VCAP (vincristine, cyclophosphamide, doxorubicin, prednisone) - AMP (doxorubicin, ranimustine, prednisone) - VECP (vindesine, etoposide, carboplatin, prednisone) in simultaneous or sequential combination, with antiviral therapy based on zidovudine and interferon-alpha, an intrathecal neuro meningeal prophylaxis, hematopoietic stem cell allograft remains a promising and potentially curative pathway for aggressive forms, for patients who are ineligible for transplantation or who have not achieved remission after chemotherapy, treatment with arsenic trioxide is initiated followed by maintenance with AZT / IFN (Marçais, 2012 and Nasr, 2014). The JCOG-LSG (Japan Clinical Oncology group-lymphoma study group) conducted a phase III trial comparing the LSG with CHOP 14 (vincristine, cyclophosphamide, doxorubicin, prednisone every 14 days), the LSG 15 was more toxic than the CHOP 14 but complete remission was greater with LSG 14 (40% vs 25%) and overall survival at 3 years was 24% in the LSG15 arm versus 13% in the CHOP arm (Tsukasaki, 2007).

Other clinical trials, mainly conducted in Japan, have demonstrated that the LSG protocol can induce acceptable complete response rates in the lymphoma form 66.7% but not in the acute form 19.6%. However, the long-term prognosis remains poor in both cases, due to a high relapse rate (Bazarbachi, 2011 and Marçais, 2012). The indolent forms (smoldering and chronic) have a better prognosis in comparison with the aggressive forms, but in the long term the survival is mediocre for the patients who are put under watchful waiting until the progression of the disease, the treatment of reference in these forms is the IFN / AZT combination with 100% overall survival at 5 years, the recommended dose is 900 mg / day of zidovudine and 5-6 million IU / m2 / day of interferon-alpha with dose reduction after one month of treatment at 600mg / day for AZT and 3-5 million IU / day for IFN or 1.5µg / kg IFN pegylated per week, this treatment is administered continuously, the relapse may occur at a standstill. The combination of arsenic trioxide and IFN / AZT is being studied and proposed in indolent forms in order to stop treatment and complete cures (Marçais, 2012).

Symptomatic treatment: The symptomatic treatment is essential and consists in the correction of hypercalcemia by hydration and bisphosphonates, the systematic prevention of pneumocystosis and fungal infections by trimethoprim sulfamethoxazole and antifungal agents respectively (Bazarbachi, 2011; Tobinai, 2004). Although cytomegalovirus infection is observed in ATL patients, ganciclovir is not routinely recommended. Prophylaxis with anti-Strongyloid agents, such as ivermectin or albendazole, should be considered to avoid systemic infection in patients with a history of past and / or present exposure and even if not yet demonstrated, the prophylaxis of the anguillulose reduces the risk of development of the ATL.

Response Criteria: The most recent tests use the criteria proposed by the Japan Clinical Oncology Group (JCOG) since 1991. The international consensus suggests a modification of the criteria of JCOG by defining the complete remission by the disappearance of all clinical signs, microscopic, and radiographic disease with less than 5% ATL cells or flower cells in the peripheral blood with an absolute lymphocyte count, including flower cells, less than 4 109 / L. Partial remission (RP) is defined as ≥ 50% reduction in lymphadenopathy size in larger measurable diameters initially without the appearance of new lesions with a 50% or greater reduction in the number of peripheral blood lymphocytes with circulating lymphocyte levels, including flower cells ≥ 4 109 / L. Relapse is defined as a 50% increase in size of lymphadenopathy or appearance of new lesions outside the skin. Stable disease is defined as a stabilization of each criterion for a period of at least 4 weeks [1,11, 21]. Currently, positron emission tomography (PET) has been integrated especially for the evaluation of complete remission [11].

Prospects: Several new therapeutic agents are being evaluated: the combination of arsenic trioxide and IFN-alpha, anti CCR4 or mogamulizumab for refractory or relapsed patients, anti-monoclonal antibodies (CD25, CD2, CD52), histone deacetylase inhibitors (HDACI) such as vorinostat, romidepsin and panobinostat (LBH589) are also promising (Nasr, 2014; Yamauchi, 2015 and Nasr, 2003). Other agents such as Bortezomib, Lenalidomide, Bendamustine, forodesine (purine nucleoside inhibitor) phosphorylase and pralatrexate (anti-folic agent) are still being evaluated (Tsukasaki, 2014; Marçais, 2012 and Shi, 2011). A phase II study evaluates the combination of intensive chemotherapy + anti CCR4 followed by allograft in aggressive non-treatable ATL, another phase III compares IFN / AZA to simple monitoring for indolent forms. The anti CD52 + anti CD2 combination is also under study (Tsukasaki, 2014).

Conclusion

Adult leukemia / T-cell lymphoma (ATL) is the first human malignancy associated with chronic infection with HTLV1 retrovirus, the prognosis is appalling due to resistance to chemotherapy and profound immunosuppression. Treatment of ATLs differs by clinical form, IFN / AZT combination has changed the evolutionary profile of leukemic forms and should be considered as the standard first-line treatment with significant improvement in long-term survival, patients with forms lymphomatous patients always benefit from induction chemotherapy in simultaneous or sequential association with antiviral therapy, allograft remains a promising and potentially curative pathway. The symptomatic treatment is essentially based on the correction of hypercalcemia and the prophylaxis of opportunistic infections. Several new therapeutic agents are currently being evaluated to prevent the occurrence of relapse including arsenic trioxide associated with IFN-alpha or monoclonal antibodies such as anti CCR4 or mogamulizumab.

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