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REVIEW ARTICLE

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LEUKEMIA / LYMPHOMA T OF THE ADULT HTLV1, A CHALLENGE FOR THE CLINIC

LEUCEMIA / LINFOMA T DEL ADULTO HTLV1, UN DESAFÍO PARA EL CLÍNICO

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REVIEW ARTICLE

ABSTRACT

Adult T-cell leukemia/lymphoma (ATL) is an aggressive disease of mature activated T cell caused by human T-cell lymphotropic virus type 1 (HTLV-1). ATL carries a bad prognosis due to intrinsic chemoresistance and severe immunosuppression. The aggressive ATL forms, acute and lymphoma, are treated with chemotherapy associated with antiretroviral agents (AZT/IFN) the acute form. However, they have failed to achieve an impact on survival, that ranges from 8-10 months, respectively. Patients with chronic and smoldering ATL forms, have a better prognosis, but long term survival is poor as well, when these patients are managed with a watchfulwaiting policy or with chemotherapy. Apparently, AZT/IFN seams to benefit these patients. Meanwhile, prevention of dissemination of HTLV-1, is a must in public health policies, performing screening in blood banks and a screening to pregnant women to reduce/avoid vertical transmission of the virus.

Key words: ATLL Cell; ATLL patient; HTLV-1 (source: MeSH NLM).

RESUMEN

La leucemia / linfoma de células T en adultos (LLTA) es una enfermedad agresiva de células T maduras activadas causada por el virus linfotrópico de células T humano tipo 1 (HTLV-1). ATL tiene un mal pronóstico debido a la quimiorresistencia intrínseca y la inmunosupresión severa. Las formas agresivas de LLTA, aguda y linfoma, se tratan con quimioterapia asociada con agentes antirretrovirales (AZT / IFN). Sin embargo, no han logrado un impacto en la supervivencia, que oscila entre 8 y 10 meses, respectivamente. Los pacientes con formas de LLTA crónicas y latentes tienen un mejor pronóstico, pero la supervivencia a largo plazo también es deficiente, tanto cuando estos pacientes se manejan con una política de espera vigilante o con quimioterapia. Aparentemente, las costuras AZT / IFN benefician a estos pacientes. Mientras tanto, la prevención de la diseminación del HTLV-1 es imprescindible en las políticas de salud pública, tanto por tamizaje del virus en bancos de sangre como a mujeres embarazadas para reducir / evitar la transmisión vertical del virus.

Palabras clave: Leucemia/linfoma de células T del adulto; Virus humano T linfotrófico tipo 1 (fuente: DeCS BIREME).

INTRODUCTION

Adult T-cell leukemia/lymphoma (ATLL) is a T aggressive lymphoproliferative neoplasm, produced by human T-lymphotropic virus[1] (HTLV-1). It is a poor diagnosis disease due to chemical resistance and severe immune suppression.

This illness was first described by Uchiyama et al. on a Japanese island[1], and only in the 80's we evidenced a HTLV-1 endemic area, in the southwest of Japan. Later, we identified another areas in the Caribbean, Central and South America, and Middle East[2]. It is believe to exist around 1 million of HTLV-1 carriers in Japan, and we estimate from 5 to 10 million of carriers worldwide[2].

In Japan, the estimated risk of developing ATLL in virus carriers is from 6% to 7% in men, and from 2% to 3% in women, and latency time for its development

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is 40-50 years old, unlike what happens with spastic paraparesis and other non-neoplastic diseases associated to HTLV-1, in which time period for development after infection is shorter.

Age of onset of disease depends on geographical area. For instance, in patients from South America, the Caribbean and United States, the diagnostic average age is 40-50 years old, whereas in Japan is 50-66 years old[3-6].

In the other hand, there is a clear predominance in men in Japan, whereas in other areas like Jamaica or some US zones exists a low women predominance[7, 8].

THE VIRUS

It was in 1979 when HTLV-1 was first isolated, using cutaneous lymphomas. Samples. It was the first retrovirus associated to a neoplasm. However, the discovery of HIV in the 80's would overshadow its study for years[9,10].

HTLV-1 transmission is mainly produced by three ways: via mother-son (in labor or breastfeeding), parenteral or sexual[11-15]. From all of them, the most important occurs at a very early age: breastfeeding with mother's milk[16].

This transmission ends up in carrying the virus. Most of carriers will be asymptomatic the rest of their life, and we estimate that only a 5% of them will develop ATLL[17]. As it has been mentioned, this only happens in adults, from 20 to 30 years post infection[18].

Pathogenesis is not entirely understood. It is thought to be a process which embrace multiple factors, such as genetic, epigenetic or viral factors[12, 19].

HTLV-1 requires complex transcriptional processes[20]. It has the ability to join and fuse with target cell (T lymphocyte). This results in a fusion between its DNA and its guest's[21]. Then, dissemination occurs through clonal expansion[22]. That is to say, acute infection produces germ line transmission from cell to cell, and after that, in a chronic phase, clonal expansion occurs[23-24].

As already mentioned, we do not exactly know the cause of leukemogenesis. ATLL results from clonal proliferation of infected cells. Regulatory proteins like Tax, Rex and HTLV-1 Basic Zipper Protein (HBZP) play a significant oncogenic role, which leads to viral persistence, stimulation, growth and further tumor development. In other words, cells in latency develop genetic abnormalities, which finally results in ATLL[25].

It should be noted that HTLV-1 virus also provokes immune system deregulation of the guest, with an increase in lymphocyte activation, making carriers more likely to get infections[26].

PREVENTION OF INFECTION

Considering that the most frequent way of virus infection is breastfeeding, its suspension has become the main prevention of infection. In a 1987 study in Nagasaki, which evaluated virus infection due to lactation, we confirmed that it decrease from 26% to 2.7% by not allowing women carriers to breastfeed[27].

Since then, the recommendation to prevent HTLV-1 infection is not to breastfeed, or to do it only for 3 months[28]. This measure, however, should be taken cautiously in low-income countries, due to the fact that it could increase child mortality[29].

We have pondered another many aspects to prevent HTLV-1 infection, which have reduced virus prevalence in Japanese endemic areas (Table 1)[30].

Table 1. Ways to prevent virus infection.

a. To carry out HTLV-1 screening to blood donors at blood banks in order to avoid transmission via transfusion.
b. To request HIV-positive mothers not to breastfeed or to do it for less than 3 months, since extended breastfeeding increases the risk of mother-to-child transmission, due to infected lymphocyte transfer to the kid.
c. Safe sex behavior in carriers; using preservatives to avoid sexual transmission.
d. To carry out HTLV-1 serology to the patient carrier's mother, brothers and children, and to conduct counselling if this tests positive.

So far there is no effective way to prevent ATLL development within virus carriers.

ADULT T-CELL LEUKEMIA/LYMPHOMA IN LATIN AMERICA

The big difference of ethnic groups in Latin America explains the great diversity of areas where HTLV-1 is endemic, even finding differences between regions of the same country[31]. There are two theories about HTLV-1 arrival to Latin America: from African slaves, or millions of years ago through Bering Strait[2].

In order to have a point of comparison, in Japan, ATLL is equivalent to 25% of peripheral T-cell lymphomas, in North America to 2%, and in Europe, 1%[30].

Latin America and the Caribbean constitute one of the regions of the world with the highest HTLV-1 infection prevalence.

Recently, Oliveira et al.[32] carried out a systemic review pf every publication about ATLL in Center and South America. The most affected regions include Colombia, Peru, Jujuy's region in Argentina and Chile, as well as Bahia, Brazil[33].

We calculate that ATLL represents a 1.1% of non-Hodgkin lymphomas, reaching 5.5% in Peru or 0.5% in Chile[34]. In Mexico, however, there is very small infected population[35]. Cases with highest prevalence observed are in Brazil, where a 1995 study by Pompo de Oliveira et al[36,37], showed 32.4% of disseminated mature T-lymphoproliferative syndromes' cases was represented by ATLL in Rio de Janeiro. In Bahia, 26.4% of studied cutaneous lymphomas corresponds to ATLL. In Peru, Gotuzzo et al[35] and Belttran et al[38], have published ATLL cases. Around 10% of non-Hodgkin lymphoma cases from Instituto Nacional de Cáncer (Peruvian Cancer Institute) in Lima, are associated with HTLV-1. In Argentina, Marín et al.[39] have described ATLL cases, especially in Jujuy's province located at northwest of the country, where HTLV-1 prevalence is the highest of the country (3.5%). In Chile, a study published in 2003 by Cabrera et al.[40] outlined 132 cases of leukemia lymphoproliferative syndromes, where ATLL was the most common disease (48%). Although, a 2012 study about 195 consecutive cases[41] of non-Hodgkin lymphoma only showed one ATLL case (0.5%).

CLASSIFICATION AND CLINICAL FEATURES

World Health Organization (WHO) in its latest version of 2016[42] classifies it as a mature T-cell neoplasm.

Shimoyama's classification[43] distinguishes four ATLL clinical subtypes (Table 1), with different clinical presentation and prognostic: 1) indolent, 2) chronic, 3) acute (or leukemia) and 4) lymphoma. The first two are considered of indolent course, whereas acute and lymphoma type are more aggressive forms.

Bittencourt et al. also proposed primary cutaneous tumor type, which is generally a subtype of the indolent ones. This may have both different clinic and prognostic [44-46].

The main ATLL clinical features are displayed in Table 2.

Table 2. Diagnostic criteria of 4 ATLL subtypes according to Shimoyama.

Feature	Indolent	Chronic	Lynphoma	Leukemia
Frequency (%)	5	5	25	65
Counting of lymphocytes (x10^9/l)	<4	≥4	<4	High
Abnormal T-cells (%) in PB	<5	≥5	≤1	High
LDH (UI/L)	<1,5 times NV	<2,5 times NV	High	High
Calcium (mg/dL)	normal	normal	High	High
Compromise the skin and/or lung	±	±	±	±
Lymphadenopathies	No	±	Si	±
Hepatosplenomegaly	No	±	±	±
CNS/bone/pleura	No	No	±	±

PB: peripheral blood, NV: normal value

Clinical features

Clinical course is very heterogeneous. Patients may present fatigue, lymphadenopathies, hepatosplenomegaly, high LDH, hypercalcemia and opportunistic infections. Skin injuries are nearly always present. They may range from generalized erythroderma, reddish plaques, papules or nodes. They are always multiple and frequently generalized. Another less frequent ATLL clinical features include: pleural effusions and ascites, central nervous system (CNS) involvement, whether of cranial nerves or meningeal. Bacterial infection, fungal or by opportunistic germs, are frequent due to immunodeficiency, which is exacerbated because of chemotherapy. It may infrequently involve the intestine.

Aggressive: Acute and lymphoma

Leukemia or acute subtype is presented with consumptive symptoms, circulating cancer cells, lymphadenopathies, hepatosplenomegaly, bone and skin injuries, hypercalcemia and opportunistic infections[47].

Lymphoma type is submitted with lymphadenopathies, without circulating cells. Patients may present skin and bone injuries, visceromegaly and hypercalcemia, but in minor measure than acute type[43].

Unfortunately, we take into account the most frequent ways, in both Latin America and Japan, representing 55-60% acute type cases and 20-25%, lymphoma type[37,43,48]. We should highlight, however, that the International Peripheral T-cell Lymphoma Project showed that 87% of aggressive types were lymphoma type[49], which should be studied in more detail.

Indolent and chronic

Chronic type may submit circulating pathological lymphocytes, and they may present sometimes skin and lung lesions, lymphadenopathies or visceromegaly. It is not associated with neither hypercalcemia nor central nervous system, bones or gastrointestinal tract involvement[43,47]. At the same time, it may differentiate into favorable or non-favorable subtypes, according to albumin and LDH levels. The relevance of distinguishing these two variables lies in that the first one does not require treatment, but the second one does. Indolent type typically displays skin or lung injuries, without any other involvement. It may have pathological cells in peripheral blood, but these represent less than 5%[43, 47].

Diagnostic

Clinically, ATLL diagnostic is not hard, and it is made based on seropositivity for HTLV-1, along with a concordant mature T-cell neoplasm, verified by histology and/ or cytology[47].

HTLV-1 seropositivity

The most commonly used method is ELISA's. Nevertheless, it does not distinguishes between HTLV-1 and 2, due to the fact that both virus share 70% of their genomic sequences. We use Western blotting for confirming the infection[50].

Peripheral blood. Diagnostic is guessed by detection of multi-lobed nucleus lymphocytes in peripheral blood. These cells called "flower type" or "flower cells" are mature lymphocytes which have multi-lobed nucleus, coarse chromatin, small or without nucleolus, and agranular and basophilic cytoplasm[51] (Figure 1). These cells are regarded as pathognomonic of ATLL. However, there is a great morphological diversity. It is usual to observe circulating immune cells. In indolent and chronic forms, lymphocytes are less pleomorphic, smaller, have bi-lobed or multi-lobed nucleus, and compact chromatin. More than 5% of abnormal T-cells in peripheral blood due to cytology and immunophenotype are enough to run ATLL diagnostic in patients without tumor lesions.

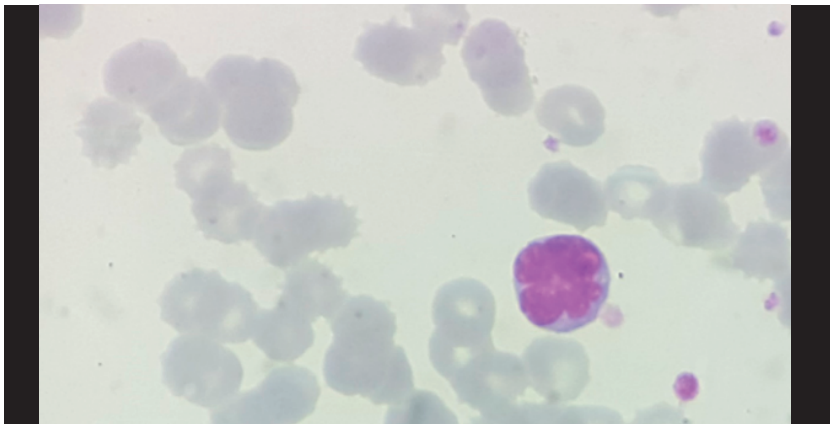

Figure 1. Flower cell in peripheral blood.

Immunophenotype

In most patients, cells in ATLL feature a mature T-cells phenotype, and they are positive for CD2, CD5, CD25 y CD45RO, T-cell receptor αβ y HLA-DR. Besides, they are negative for CD7, and CD3 may be weak. Almost 90% of cases are positive CD4 and negative CD8 (42, 52). C-C chemokine receptor type 4 (CCR4) is submitted in more than 90% of cases, and it is associated to poor diagnosis.

Bone marrow

Generally, a bone marrow aspiration or biopsy is not required for diagnostic. However, it may provide useful data about bone marrow reserve, before chemotherapy.

Biopsy of affected sites

When diagnosis cannot be run in peripheral blood, we recommend lymph node biopsy by excision, not by puncture. Although, histology of skin and lymph are not specific of ATLL.

Immunohistochemistry study demonstrates that cells are positive for CD3, CD5, CD25, and generally for CD4, and negative for CD7 y CD20. Around 5% of them are positive for CD8[42].

Biochemical alterations

Hypercalcemia is the most typical ATLL lab alteration, unlike other chronic lymphoproliferative syndromes. It can be observed in half of acute form cases and in 20% of lymphoma form. It is not observed in neither indolent nor chronic form. Elevated serum LDH and β2 microglobulin are frequent alterations and they reflect tumor activity and mass burden. The soluble form of α chain from interleukin-2 receptor (IL-2) is elevated in a similar way.

Radiological images and endoscopy

Computed axial tomography of the neck, thorax, abdomen and pelvis, is necessary for detecting sites of nodal or extranodal involvement. An upper gastrointestinal endoscopy with biopsy should be considered, because gastrointestinal tract involvement in aggressive ATLL is frequent. We should consider CNS review by images and/or lumbar puncture due to brain/meningeal involvement by ATLL or opportunistic infections.

Risk stratification

3 systems of prognostic stratification have been reported in terms of this disease: ATL-PI, JCOG-PI y modified ATL-PI. The first one was validated in a Japanese cohort of 807 patients with lymphoma and acute type. This divided patients in 3 groups according to 5 factors: Ann Harbor classification, Performance Status (PS), age, albumen and soluble IL-2 receptor[53]. JCOG-PI score analyze 276 patients enrolled in different studies from Japanese group: Japan Clinical Oncology Group – Lymphoma Study Group (JCOG-LSG). This group divided patients in 2 groups: high risk, anyone who had one or more of the following factors: PS>2, elevated calcemia (54). Modified ATL-PI analyzed 1792 patients. Evaluated variables were acute type, poor PS, high levels of soluble interleukin-2 receptor (>5000U/mL), corrected calcemia >12 mg/dl, and C-reactive protein levels > 2,5mg/dl[55].

In many Latin American countries, we do not count on measurement of soluble IL-2 receptor levels, a reason why it could not be a viable alternative. A more-easy-to-perform prognostic score in our reality is IPI, which has already been validated in other studies in patients with lymphoma type ATLL[49].

Prognostic

Generally, ATLL is marked by a poor diagnosis, with short survival[56]. One of the factors that most contributes is chemoresistance and immunosuppression associated to ATLL, especially in its aggressive forms[57].

In Japan, median global survival skirts 12 months, even in intensive chemotherapies[58]. A study carried out by Katsuya et al[59] stated 1594 patients treated with current therapies. This study reported a global survival of 8.3, 10.6, 31.5 and 55 months for acute, lymphomatous, chronic and indolent form, respectively. Another study, carried out in New York, reported an global survival of only 24 weeks (5). In addition, in a retrospective study, survival for 5 years was 14%[56].

Treatment

Most of patients cannot achieve to be cured with current therapeutic options, besides, survival has not improved significantly in the last 20 years. It must also be considered that most clinical studies are performed in Japanese population, thus we do not know if they are studies completely replicable to our patients. In fact, we have noted differences in results when comparing with population of studies performed in US[60].

Therapeutic options

Current therapeutic options for ATLL include: observation until progression (watch and wait), interferon alpha (IFN), zidovudine (ZDV), combination chemotherapy, allogeneic transplantation of hematopoietic stem cell and new agents.

However, there is no standard treatment for ATLL nowadays. Hence, before any specific recommendation, we encourage trying with clinical studies[61].

Observation

Patients with indolent and chronic forms can survive one or more years without chemotherapy. We agree that in indolent forms, this active observation strategy could be used[51].

Conventional chemotherapy

The most used chemotherapy is the so-called CHOP-like, especially in lymphomatous form. Between 1970 and 1980, it was treated the same way that with other T-cells, reaching 8 months survival. In 1998, a phase III study[62] was carried out. This study compared CHOP 14 (cyclophosphamide, doxorubicin, vincristine and prednisone), with VCAP–AMP–VECP (VCAP: vincristine, cyclophosphamide, doxorubicin and prednisolone; AMP: doxorubicin, ranimustine and prednisone; VECP: vindesine, etoposide, carboplatin and prednisone). Even though the second one obtained the higher toxicity, it achieved the most complete answers (40% vs 25%, P = 0.02) and the most global survival up to 3 years (24% vs 13%). For this reason, it is considered as a standard currently, however, many of the drugs of this scheme are not found in Latin America.

Due to the high percentage of CNS involvement, we recommend intrathecal prophylaxis along with chemotherapy[63].

Antiretroviral therapy and interferon alpha

Several studies have made use of the following combination: antiretroviral agent, zidovudine (ZDV) and IFNα (ZDV/IFN)[64-67]. A current meta-analysis[68] showed similar survival to the ones obtained with chemotherapy in non-lymphomatous forms, including acute form. This analysis reviewed 254 ATLL patients treated in USA, United Kingdom, France and Martinique, between 1995 and 2008. The study demonstrated benefits of an early intervention in ATLL patients treated with IFNα/ZDV. 5-years global survival (GS) was 46% for 75 patients who received first-line antiretroviral therapy, 20% for 77 patients who received first-line chemotherapy, and 12% for 55 patients who received first-line chemotherapy followed by antiretroviral therapy. Patients with chronic, indolent and acute ATLL benefitted significantly from first-line antiretroviral therapy, whereas patients with lymphoma did not get benefitted from this strategy. In patients with indolent and chronic ATLL, 5-years GS resulted 100%, in acute form was 28% compared with 10% of those treated with first-line chemotherapy On the other hand, in patients with lymphoma, 5-years GS was 0% compared with 18% of those treated with first-line chemotherapy. Although it has regular tolerance, western guidelines recommend this combination in ATLL, except in lymphoma type. Japanese guidelines do not recommend this routine due to poor evidence, though[69].

Hematopoietic stem cell transplantation

Autologous transplant has not proved to be useful in this kind of patients, due to a high rate of recurrence[70]. Allogeneic transplant, however, has proved to be able to induce long-term survival in a 25-40% of patients. Nevertheless, high toxicity of this procedure, up to 40% of mortality, forces to be careful with this strategy. A retrospective study showed an analysis of 586 patients where an allogeneic transplant was performed. 36% of patients was alive after 3 years, with median GS of 9.9 months. In addition, there was a low tendency towards a better survival in elderly patients with regime of reduced intensity[71]. Another Japanese retrospective study showed a 3-years GS of 33% in patients with allogeneic transplant[72]. On the other side, there is data from a current systematic review, which showed 73% of complete remission in these patients, but with high rates of relapse[73].

Due to these results, American Society for Blood and Marrow Transplantation recommends in its guides first-line allogeneic transplant in young patients with acute or lymphoma type ATLL[74].

In brief, observation in asymptomatic patients may be appropriate for chronic or indolent ATLL. If they are symptomatic, it could be treated with local therapy (dermatological) or ZDV/IFN. In chronic type, we have seen that chemotherapy may worsen its course, in comparison with observation[75].

We recommend to enroll in clinical study for non-favorable chronic type. If this is not possible, another option is treatment with AZT/IFN or chemotherapy.

In lymphoma type, we suggest admission to clinical study. If this is not possible, we recommend CHOP-like regimes[62].

Monoclonal antibodies

Recently, in Japan, it has been approved the monoclonal antibody (mAB) anti-CCR4 (mogamulizumab) which acts against C-C chemokine receptor type 4 (CCR4), that is expressed in cancer cells of most of patients with ATLL[76-78]. It is mainly used in refractory patients by this time. This stage showed response rates of 11% vs 0% in patients with other therapies defined by the treating doctor[79].

Supportive treatment

We recommend prevention of opportunistic infections in patients with ATLL, with prophylaxis of sulfamethoxazole/trimethoprim and antifungal agents. In endemic areas, anti strongyloides agents, such as albendazole, should be considered.

Relapse

This population has very limited therapeutic options. For the moment, we only recommend admission to clinical studies. You can try allogeneic transplant in patients without complete remission, but results are very poor[71-72].

CONCLUSION

ATLL is still a poor diagnosis disease, worse than other T-cells. We do not observe plateau in survival curves with current treatments, in aggressive or indolent forms of ATLL, treated with chemotherapy or observation, and/or ZDV/IFN. Use of monoclonal antibodies, such as mogamulizumab associated to intensive chemotherapy has shown improvement in survival of patients with aggressive ATLL. Allogeneic transplant may achieve to cure a small number of young patients, despite a considerable mortality related to transplant. We expect new agents to join the treatment of this serious disease. Meanwhile, the efforts to prevent HTLV-1 dissemination should be maximized, making a great public health effort in order to improve surveillance of virus, along with screening in blood banks, and requesting it in birth control to significantly reduce vertical transmission of the virus.

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