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TABLE OF CONTENTS

Original Studies

Penile Cancer in India: A Clinicoepidemiological Study ................................................................. 07
M. Pahwa, M. Girotra, A. Rautela, R. Abraham

Gastric Cancer: A Retrospective Analysis from AIIMS, New Delhi ....................................................... 11
R. Hadi, B.K. Mohanti, S. Pathy, G.K. Raah, N.K. Shukla, S.V.S. Deo, A. Sharma, V. Raina

Review Articles

Intensity Modulated Radiotherapy (IMRT) In Head and Neck Cancers – An Overview ................................. 17
C.M. Nutting

Adult T-Cell Leukemia/Lymphoma ............................................................................................................ 27
K.I. Rasul, Z.A. Barwari

Case Reports

Adrenocortical Tumors in Children: A Kuwait Experience ......................................................................... 38
R. Mittal, D. G. Ramadan, N. M. Khalifa, S. O. Khalifa, Z. Mazidi, M. Zaki

Limb Sparing Surgery in Soft Tissue Sarcoma of Extremities: An Indian Perspective ..................................... 47
R.V. Bhargavan, P. Kumar, K.C. Kothari

Mixed Germ Cell Tumor of Ovary and Clitoreomegaly in Swyer’s Syndrome: A Case Report ..................... 55
S. Aminimoghaddam, B. Mokri, F. Mahmoodzadeh

Palmar Fasciitis and Arthritis Syndrome Associated With Metastatic Ovarian Cancer: A Paraneoplastic Syndrome ............................ 59
I.K. Nahar and M. S. Al-Rajhi

Trichilemmal Pilar Tumor of the Scalp: A Case Report .............................................................................. 62
K. Al Saleh, H.S. Hooda, H. El-Wakiel, R. Safwat, A. Bedair, W. Eskaf

Carcinosarcoma of Renal Pelvis with Immunohistochemical Correlation .................................................. 65
S.D. Deshmukh, V.L. Gaopande, D.P. Pande, G.S. Pathak, B.K. Kulkarni

5-Flourouracil Cardiotoxicity – An Elusive Cardiopathy: Case Report ....................................................... 70
G. M. Bhat, M. H. Mir, H. I. Showkat, B. Kasanna, F. Bagdadi, A. H. Sarwast, S. Quadri

An Unusual Variant of Prostatic Adenocarcinoma with Metastasis to Testis: A Case Report ....................... 73
K. R. Anila, T. Somasathian, A. Mathews, K. Jayasree

Mammary Fibromatosis in a Male Breast ..................................................................................................... 77
N. Al-Saleh, T. Amir, J. N. Shaf

Primary Isolated Extramedullary Plasmacytoma of Mesentry: A Rare Case Report ...................................... 81
R. Galhotra, K. Saggar, K. Gupta, P. Singh

Feature Article

Balsam Organization for rehabilitation and support for cancer patients and their families .................................. 85

Conference Highlights/Scientific Contribution

• Conference Highlights – 1st Palliative Care Conference in Kuwait .................................................................. 86
• News Notes .................................................................................................................................................. 89
• Advertisements ........................................................................................................................................... 91
• Scientific events in the GCC and the Arab World for the 2nd Semester of 2012 .............................................. 92
Adult T-Cell Leukemia/Lymphoma
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Abstract
The adult T-cell leukemia/lymphoma (ATLL) syndromes comprise neoplasms that arise in peripheral lymphoid tissues but a high frequency present with blood involvement mimicking T-cell leukemia. Clinically ATLL is sub-classified into four groups: acute, lymphomatous, chronic and smoldering. ATLL is etiologically linked to the human T-cell lymphotropic virus type I (HTLV-I). The diagnosis of ATLL is based upon a combination of characteristic clinical manifestations, morphological and immunophenotypic changes of the malignant cells, in addition to the confirmation of HTLV-I infection. ATLL is an aggressive malignancy with a median survival of less than 12 months and no successful treatment yet available. Patients are either refractory or only transiently respond to chemotherapy or purine analogues. Smoldering and chronic ATLL pursue an indolent course and survival for years until the disease progresses and becomes refractory to therapy. The major causes of death in ATLL are opportunistic pulmonary infections and progressive disease, often in association with hypercalcemia.

Keywords
Adult T-cell leukemia/lymphoma, HTLV-1, Cutaneous T-cell lymphomas, pneumocystis jirovecii (Carinii) pneumonia and Hypercalcaemia

Introduction
The leukaemia/lymphoma syndromes comprise neoplasms that arise in peripheral lymphoid tissues but a high frequency present with blood involvement mimicking T-cell leukemia. These include Sézary Syndrome (SS) and Adult T-cell lymphoma/leukemia (ATLL). In the REAL and WHO classifications, the ATLL is considered as a peripheral T-cell neoplasm associated with infection by the human T-lymphotropic virus, type I (HTLV-I)(1,2). It is a highly aggressive T-cell non-Hodgkin’s lymphoma (NHL) variant. The most common presentation of ATLL is an acute onset bone marrow and peripheral blood involvement with a high white blood cell count and circulating lymphocytes with characteristically abnormal convoluted nuclei, hypercalcemia, lytic bone lesions, cutaneous lesions (often simulating those seen in mycosis fungoides), generalized lymphadenopathy, hepatosplenomegaly, interstitial pulmonary infiltrates and central nervous system involvement in some patients. Clinically ATLL is sub-classified into four groups: acute, lymphomatous, chronic and smoldering. The acute form typically involves multiple organs (including the central nervous system), the skin, a leukemic peripheral blood picture, hepatosplenomegaly and systemic lymphadenopathy. Lytic bone lesions are often present with hypercalcemia. The peripheral blood leukemic cells are multilobated lymphocyte “flower cells,” with a T-helper cell immunophenotype and expression of CD2, CD3, CD4, CD5 but not CD8. CD7 expression is often lost. The strong expression of CD25 (interleukin-2 receptor) is characteristic of ATLL and helps to distinguish this disorder from cutaneous T-cell lymphoma(3). The prognosis is poor, although patients may respond initially to treatment with combination chemotherapy regimens devised for advanced aggressive NHL. Relapses are common, with a median survival of eight months and a four-year survival of 12 per cent (4).

Aetiology
It has been found that infection with the human T-cell lymphotropic virus type I, a retrovirus, can cause a distinctive hematological malignant
disease, ATLL. The human T-cell lymphotropic viruses’ type I and II (HTLV- I / HTLV- II) belong to a group of oncogenic retroviruses known to be pathogenic to human. ATLL was first described as a clinical entity in 1977. Its association with HTLV - I was demonstrated in the early 1980s almost simultaneously in the USA and Japan, based on sero-epidemiological studies and the isolation of HTLV - I from ATLL cells. HTLV-I was discovered in 1980 and was shown be associated with the etiology of adult T-cell leukemia/lymphoma (ATLL), a progressive autoimmune-like neurological disorder known as tropical spastic paraparesis or HTLV-1 associated myelopathy and autoimmune like rheumatic disorders (5).

HTLV-1 was known to be endemic in certain Afro-Caribbean countries and in Europe and America the virus is more commonly found in populations that have emigrated from such endemic areas (6).

Epidemiology

ATLL is etiologically linked to the human T-cell lymphotropic virus type I (HTLV-I). (7,8,9) HTLV-I, a retrovirus, known to be endemic in southern Japan and the Caribbean basin and occurs sporadically in Africa, Latin America, the Middle East, and the United States. (10-14) Adult T-cell leukemia–lymphoma occurs in less than five percent of people with HTLV-I infection, with an average latency period of more than 30 years (15,16). A cellular immune deficiency in affected patients allows opportunistic infections to develop (17,18). In the State of Qatar, screening for HTLV-I commenced since early nineties and the modified screening assays that include screening for both HTLV-I and HTLV-II were adopted as soon as they became available however later, it was not possible to work out the actual prevalence of HTLV infection among donors (19). There are few reports from the Middle East about the prevalence of HTLV1 virus infection and only occasional case report of ATLL(20, 21). Incidence of ATLL varies by population according to the prevalence of HTLV-I infection. It varies from 0.05 per 100,000 population to 0.5 per 100 000 population in certain endemic areas like Jamaica and Caribbean area. ATLL affects adults without sex predominance. Age of affected population at diagnosis varies in different geographical areas; and it varies between the 4th to the 6th decades of age.

Pathogenesis

HTLV-I infection is the primary cause of ATLL in 100 percent of cases. This infection is thought to play a significant role in the pathogenesis of ATL (22). Very long latency between the infection and the development of the malignancy may involve other aetiological factors but these are still unclear. In all malignant cells in an affected individual, the HTLV-I pro-viral genome is incorporated into an identical location of the genome. This happens before clonal expansion of the malignant cells. Whether the particular insertion location affects the phenotype of the cell is unclear. Actually ATLL development among HTLV-I infected individuals is relatively low. The long-term risk of developing ATLL following infection with HTLV-I in endemic areas has been estimated to be 4 to 5 percent, usually after a latency period of several decades. Exposure to the virus early in life increases the risk of eventual development of ATLL. A shorter latency period has been noted in infected patients receiving treatment with immune-suppressive agents for other reasons (23-28). How this virus lead to the development of the tumor is not clear, but it may be related to the viral regulatory gene TAX (Trans Activating gene of the X region) which encodes an oncoprotein known as tax protein. This gene product induces cellular proliferation and prolongs cell survival and prevents DNA damage (28).

Hypercalcaemia is commonly associated with ATLL and sometimes may be severe; it is aparaneoplastic manifestation of ATLL. It usually results from certain cytokine production as parathyroid hormone related protein (PTH-RP) tumor necrosis factor-beta or interleukin-1 and increased expression of the receptor activator of nuclear factor KB (RANK) ligand gene. This leads to abnormal high uptake in bone scan described as super scan of the bone in radionuclide study and elevated serum alkaline phosphatase (29-30).
Clinical Manifestations

The clinical features of ATLL are variable - from the most common generalized lymphadenopathy to rare manifestation of central nervous system involvement. Clinical variants have different clinical course (31):

1. Acute type (60%) - this is the most common clinical variant at presentation. Patients with the acute variant of ATLL most frequently present with systemic symptoms, organomegaly, lymphadenopathy, an elevated lactate dehydrogenase (LDH) level, and circulating malignant cells. It has a poor prognosis and survival is usually short measured in months despite aggressive treatment.

Common presenting signs or symptoms include generalized lymphadenopathy in almost all cases. Hepatosplenomegaly in about half of the patients. Bone marrow involvement in nearly one third of the cases. A high peripheral blood white blood cell count is common due to the presence of circulating lymphocytes with distinctively abnormal convoluted nuclei. One-half of the patients will have hypercalcemia with or without lytic bone lesions at presentation and an additional third will develop hypercalcemia at some point during the course of their disease. Maculopapular skin lesions occur nearly in nearly half of the cases (32-34) (Figure. 1).

2. Lymphomatous variant (20%) - this is characterized by prominent lymphadenopathy without blood involvement. Patients frequently have elevated LDH levels and can have hypercalcemia. Prognosis is poor with a survival which is usually short (in months) despite of aggressive treatment as in the acute variant.

3. Chronic variant (15%) - these patients are characteristically have an increased white blood cell count with absolute lymphocytosis which may be stable for months to years, skin lesions and only mild lymphadenopathy. These patients have no hepatosplenomegaly or hypercalcemia and a normal or only slightly increased LDH level (less than twice the upper limit of normal). This variant has a better prognosis than the acute and lymphomatous variants with survival measured in years (35).

4. Smoldering variant (5%) is the least common; these patients are often asymptomatic except for frequent skin and/or pulmonary lesions. They have normal blood lymphocyte counts with less than 5 percent circulating neoplastic cells and normal calcium levels. The prognosis is good and average survival is more the 5 years.

In general the frequency and severity of the hypercalcemia and lytic bone lesions varies widely among the variants of ATLL. Hypercalcemia related features like renal impairment and neurological manifestation may be among the presenting features of ATLL. The incidence of hypercalcemia in the acute type is approximately 70 percent at some point in their disease course while 40 percent of them might develop lytic bone lesions (36,37).

Opportunistic infections may occur in ATLL and may be fatal in some cases; these include pneumocystis Jirovecii (Carinii) pneumonia, cryptococcal meningitis, strongloides stercolaris and disseminated herpes zoster (38).

These are more common in acute, chronic and smoldering variants than in the lymphomatous type. In some cases the clinical manifestation

Figure 1. ATLL patient with the characteristic Maculopapular skin rash
occurred sequentially over a period of time despite typical ATLL peripheral blood, bone marrow and flowcytometric features (39,40).

**Diagnosis**

As in most hematological malignancies the diagnosis of ATLL is based upon a combination of characteristic clinical manifestations, morphological and immunophenotypic changes of the malignant cells and additionally, the confirmation of HTLV-I infection.

1. **Peripheral blood** About 75 percent of patients have circulating lymphoma cells, which are very characteristic of the disease (41,42, 43). It is a feature which gives a greater value to the examination of peripheral blood as compared to bone marrow aspirates or trephine biopsies in guiding initial diagnosis. Peripheral blood films show a pleomorphic picture with the presence of cells having different size and degree of nuclear irregularities in the acute and chronic leukaemia subtypes. The archetype cell, designated as ‘flower cell, is usually a medium-sized lymphocyte with condensed chromatin and a convoluted or polylobated nucleus44 (Figure 2).

   A number of cerebriform cells may be present but the degree of pleomorphism usually permits easy differentiation from Sézary syndrome. The mild degree of marrow infiltration usually results in little anaemia or thrombocytopenia at presentation. Eosinophilia is not infrequent(45).

2. **Bone marrow biopsy** may reveal mild or no lymphoid infiltration but bone resorption and osteoclast proliferation is not uncommon, especially in patients with hypercalcaemia. Patients with leukaemic presentation may show a variable degree of marrow infiltration by the characteristic neoplastic cells. The pattern of marrow involvement may be interstitial, random focal or diffuse. Occasionally it is paratrabecular. The degree of marrow infiltration at presentation is usually mild. The character of the infiltrate is highly variable between cases. Many cases show considerable variation in cell size with nuclei varying from medium size to large. Other cases either have predominantly small or predominantly large cells. In the larger cells, nuclei tend to be vesicular with distinct nuclear membrane and two to five distinct nucleoli; smaller cells often show chromatin condensation. Nuclei vary in shape, being round, oval, indented, deeply lobulated or convoluted. Giant cells may be present; some of these resemble Reed – Sternberg cells while others have nuclear convolutions, coarsely aggregated chromatin and prominent nucleoli (Figure 3) (46).

3. **Immunophenotyping:** Immunological markers of ATLL cells are those of mature activated T – cell. In most cases, cell immunophenotype is (CD2 +, CD5 +) and (CD7 –, CD8 –). CD3 is expressed in the cytoplasm. CD30 may be positive.
and TCR genes are clonally rearranged. In some cases, the cells lack expression of CD3 and TCR in the membrane. It is thought that the reduced CD3 and TCR molecule expression in ATLL cells results from retroviral induced cell activation and that it might play a role in disease pathogenesis. Most ATLL cells have a CD4+ CD8− phenotype. Other phenotypes such as CD4 + CD8 + or CD4 − CD8 + have been reported uncommonly and seem to be associated with a more aggressive disease behavior. A distinctive feature of ATLL cells is the strong expression of the IL-2 receptor (CD25) in the cell membrane. Soluble IL-2 receptors are detected in the patient’s serum and the levels correlate with tumour burden and response to therapy. Other markers linked to T-cell activation such as HLA-DR determinants and CD38 are expressed in a variable proportion of cases but NK markers are negative (47, 48).

4. Immunohistochemistry: The neoplastic cells are positive for CD2, CD3, CD5 and typically also CD25. In most cases, they are CD4 positive. Large cells may be CD30 positive (49).

5. Serology: The demonstration of HTLV-I antibodies in the patient’s serum is the key test for the definitive diagnosis of ATLL. These antibodies are usually detected using enzyme-linked immunosorbent assay (ELISA). Western blot (WB) is used as confirmatory testing and distinguishes between HTLV-I and the less pathogenic HTLV-II in almost all patients suspected of having the disease. In a small number of cases, the clinical and laboratory features are highly suggestive of ATLL, but HTLV-I cannot be detected by either serology or molecular analysis. In these situations the diagnosis of ATLL should be critically reviewed such cases might need to Polygonase chain reaction (PCR) testing to detect proviral DNA in the tumor cells when the serology is negative.

6. Cytogenetics and molecular analysis: ATLL does not seem to have a discrete chromosomal abnormality and although most cases tend to have an abnormal karyotype, however, no consistent defect has been reported. Complex karyotypic and clonal abnormalities are well recognized in ATLL. The most frequent derangements comprise: +3, +7, +21, monosomy X, deletion of chromosome Y and rearrangements involving 6q and 14q. Rearrangements of chromosome 14 at breakpoints q11 and q32, characteristic of T-PLL, are rare. Mutations of the tumor-suppressor genes TP53, CDKN2A (encoding the p16INK4A protein) and CDKN2B (encoding the p15INK4B protein) have been documented and implicated in development of the disease. In smoldering ATLL, clonal and non-clonal abnormalities have been reported and occasional cases show clonal evolution from the smoldering to the acute phase (50). Sequential cytogenetic studies spanning the various phases of HTLV-I infection, from carrier status till the clinically manifested acute ATLL, might give some clues to the steps involved in leukaemogenesis, as other factors involved in the neoplastic transformation of HTLV-I-infected lymphocytes are still largely undiscovered.

Differential Diagnosis

The differential diagnosis of ATLL arises with primary T-cell leukaemias and T-NHL not associated to HTLV-I. ATLL needs to be differentiated from cutaneous T-cell lymphoma (CTCL), such as mycosis fungoides and Sézary syndrome. Immunophenotyping may be helpful in distinguishing the two types of the CTCL, which are CD4+ and CD7-, from ATLL more have a distinctively strong positivity for CD25. The key differentiating feature is the presence of HTLV-I in the malignant cells of ATLL. T-cell leukaemias and T-NHL can be distinguished from ATLL by clinical features, morphology and the presence or absence of HTLV-I. The HTLV-I test is essential, as ATLL-lymphoma type, or its cutaneous form, cannot be distinguished from other T-NHL or MF/SS when only histology is available. In endemic areas
and when the picture is not typical of ATLL, DNA analysis is needed in addition to serology to confirm that HTLV-I is clonally integrated in the leukaemic cells. The distinction between smoldering ATLL and carriers of the retrovirus is based on molecular analysis with probes specific for HTLV-I that will show a monoclonal/oligoclonal pattern of retroviral integration in smoldering ATLL versus a polyclonal pattern in the carriers. Like ATLL, T-prolymphocytic leukemia (T-PLL) is an aggressive malignancy characterized by circulating malignant T lymphoid cells, marked lymphocytosis, cytopenias, and splenomegaly. Immunophenotype can help distinguish this disorder from ATLL. Both ATLL, T-PLL are CD4+, however, unlike ATLL, T-PLL is CD7+ and CD25-. HTLV-I is not incorporated into the genome of the malignant cell, and more than 80 percent of patients will have genetic abnormalities, usually an inversion of chromosome 14, which fuse the TCL1 gene to the T-cell receptor (TCR) alpha/delta locus and lead to the over expression of TCL1 protein.

Anaplastic large cell lymphoma (ALCL) is another T-cell lymphoid neoplasm which primarily involves the lymph nodes and skin but can demonstrate circulating malignant cells. Cell morphology is varied and the immunophenotype is CD4+ and CD7- much like ATLL. Immunohistochemistry staining can be of help since ALCL has strong, uniform expression of CD30 with a membrane and golgi distribution and is cytotoxic granule-associated protein positive. ALCL diagnosis can be confirmed by demonstrating an ALK1 gene rearrangement or expression of the Alk-1 protein, neither of which can be found in ATLL. However, the cutaneous variant of ALCL is less likely than the systemic variant to demonstrate ALK1 positivity. In addition, HTLV-I is not incorporated into the genome of the malignant cell in ALCL.

Angioimmunoblastic T cell lymphoma (AITCL) is also one of the peripheral T cell lymphomas and has features similar to ATLL like lymphadenopathy hepatosplenomegaly, bone marrow involvement, and a pruritic skin rash. Most patients demonstrate a polyclonal hypergammaglobulinemia. The morphology of the malignant cells is varied but one common feature is the prominent arborizing high endothelial venules not typically found in ATLL. Immunophenotype typically demonstrates CD4 positivity and decreased intensity of CD7. Unlike ATLL, HTLV-I is not incorporated into the genome of the malignant cell in ALCL.

Treatment

Before starting treatment it is recommended that lumbar puncture should be done for all patients with acute or lymphoma-type variants but may be performed at the start of therapy if intrathecal chemotherapy is a component of the treatment regimen. Cerebrospinal fluid should be sent for cytology and/or flowcytometry.

A contrast-enhanced computed tomography (CT) scan of the neck, chest, abdomen and pelvis should be performed as part of staging work up as in any case of lymphoma. The FDG-avidity of ATL is not well established and may be variable. As such, positron emission tomography (PET) scanning is reserved for use in clinical trials.

ATLL is an aggressive malignancy with a median survival of less than 12 months and no successful treatment is yet available. Patients are either refractory or only transiently respond to chemotherapy or purine analogues. Smoldering and chronic ATLL pursue an indolent course and survival for years until the disease progresses and becomes refractory to therapy. While the acute, lymphomatous type and the unfavorable chronic variants, survival without treatment is counted in days to weeks and there is no need to start immediate treatment. The poor outlook of ATLL relates to both chemotherapy resistance and disease complications (hypercalcaemia and opportunistic infections). Despite major advances in disease pathogenesis, the management of these patients remains a challenge. The two main approaches to treatment are combination chemotherapy and a combination of Zidovudine (AZT) and interferon.

Although initial anthracycline-based combination chemotherapy results to response rates approximating 70%, only one-third of treated patients achieve a complete remission (CR). Most patients being refractory or achieve transient responses to CHOP. Based on the International
Peripheral T-Cell Lymphoma Project analysis of patients with adult T-cell leukemia/lymphoma, there was no overall survival benefit for those patients receiving an anthracycline-containing regimen. Despite its limited efficacy, cytotoxic chemotherapy remains the mainstay of therapy for this disease. In Japan, a randomized phase III trial using vincristine, cyclophosphamide, prednisolone, and doxorubicin (VEPA) versus VEPA plus methotrexate (VEPA-M) resulted to a complete response rate of 37 percent in the VEPA-M arm compared to 17 percent in the VEPA. The median survival however, was 6 months \(^{(57,58)}\). Another phase II Japanese study tested LSG 15 administered with granulocyte colony-stimulating factor support to patients with treatment-naive aggressive adult T-cell leukemia/lymphoma. An eight-drug regimen using vincristine, cyclophosphamide, doxorubicin, prednisone, ranimustine, vindesine, etoposide, and carboplatin resulted to a median survival of 13 months \(^{(59)}\). A combination trial of pentostatin, vincristine, doxorubicin, etoposide and prednisolone resulted to 28 percent complete responses; the median survival was, however, only 7.4 months \(^{(60)}\). Irinotecan is a modestly active drug in adult T-cell leukemia/lymphoma, with a response rate of 30 percent in a phase II trial. Its major toxicities included leucopenia (83%), nausea (69%), and diarrhea (62%) \(^{(61)}\).

Immunotherapy has been used with encouraging results in patients who received passive monoclonal and/or radiolabeled monoclonal antibodies specific to antigens expressed by the neoplastic T cells, such as CD25 (the IL-2 receptor molecule). Data with alemtuzumab is scanty. Encouraging responses have been observed in patients who received passive immunotherapy or radioimmunotherapy using monoclonal antibodies specific for antigens expressed by the neoplastic T cells, such as CD25 \(^{(62,63)}\). Even in pretreated patients, complete responses to denileukin diftitox have been observed \(^{(64)}\). A major advance in treatment comes from the use of interferon alfa and the antiretroviral agents AZT and lamivudine, either alone or when used after, or combined with, chemotherapy. Following two initial Phase II trials, two prospective studies in France and England confirmed the efficacy of this combination and documented a response rate of 65 – 92%, half of which were CR, with improved survival. Although the mechanism of action of AZT is unknown, in vitro studies suggest that the drug inhibits telomerase function and leukaemic cells enter senescence. Of 15 patients with adult T-cell leukemia/lymphoma who received \(\alpha\)-interferon and AZT, a median survival for all 15 patients was 18 months; median survival for non-responders was 6 months, and the 6 patients with partial responses were alive 8 to 82 months from diagnosis, with 55% of all patients being alive at 4 years \(^{(65)}\).

Because of its chemoresistance and its viral leukemogenesis, ATLL has been a unique disease for investigating therapy. Interferon-\(\alpha\) plus AZT has had a higher response rate (67 to 92%) than chemotherapy regimens in ATLL. A median survival of 17 months was reported in a study in which patients were debulked with two cycles of CHOP followed by AZT/IFN plus etoposide \(^{(66)}\). NF-\(\alpha\)B inhibition has been proposed as a therapeutic target in ATLL, and preliminary data have shown in vitro activity of the proteasome inhibitor, bortezomib, and the histone deacetylase inhibitor, depsipeptide. Consolidation with high-dose therapy and autologous or allogeneic SCT should be considered in young patients. Allogeneic SCT was first reported as a curative option in ATLL in 1996. Although the median survival with the SCT does not appear superior to other therapy (9.6 months in a review of 40 patients from seven centers), the 3-year estimated overall survival of 45.3% and relapse-free survival of 33.8% do suggest that SCT may offer the best chance for long-term survival \(^{(67,68)}\). Likewise, allogeneic stem cell transplantation in 10 patients resulted to a median disease-free survival of greater than 17 months although the transplantation-related mortality was (40%) \(^{(67,68,69)}\).

Despite the new therapies under investigation in ATLL, the ultimate goal is prevention of the disease. Avoiding breastfeeding in mothers infected with HTLV-1 can reduce infection in the newborn by 80% \(^{(67)}\). Other proposed methods to prevent ATLL are antiretroviral therapy, monoclonal antibody therapy, and a Tax-targeted vaccine.
Treatment of Recurrent or Refractory Disease

We do not have much information on the treatment of recurrent or refractory ATL. There are some studies which include the use of antiviral agents or antibody therapy. The benefit of antiviral agents in ATL is controversial. The HTLV-1 virus is thought to be in a latent state in patients with ATL and so antiviral agents, if active, would be expected to act through a mechanism other than antiviral activity (70). A 2010 meta-analysis of zidovudine (AZT) plus interferon alpha incorporated data from 245 patients with acute, chronic, smoldering and lymphoma-type ATLL. (71,72) AZT plus interferon alpha, Chemotherapy AND Chemotherapy followed by antiviral therapy. Patients with acute, chronic, and smoldering ATLL appeared to benefit from first-line antiviral therapy, whereas patients with lymphoma-type ATL did not. For patients with chronic or smoldering ATLL, this combination resulted to 100 percent five-year survival. Based on the results of this retrospective analysis, the investigators claimed this combination regimen as the first-line therapy in leukemic subtypes of ATLL. While encouraging, this approach needs further study before it can be widely applied. Limited experience with the anti-CD52 antibody alemtuzumab has been reported (73,74). Arsenic trioxide with or without interferon alpha and all-trans retinoic acid (tretinoin) has been used in some cases. Other new agents for the potential application to the treatment of ATLL include pralatrexate (anti-folate), bortezomib (proteasome inhibitor), forodesine (purine nucleoside phosphorylase inhibitor), histone deacetylase inhibitor, and lenalidomide (75-81).

Prognosis

Despite combination chemotherapy which can yield brief responses, median survival rate for the acute and lymphomatous variants is short (2 weeks to less than 1 year), while the chronic and smoldering forms behave more indolently regardless of therapy, but can progress to an acute phase. Tumour bulk, clinical subtype, age, performance status, serum calcium, lactate dehydrogenase levels, high β2- microglobulin, high serum soluble CD25, high serum neuron-specific enolase and a high proliferation fraction are major prognostic indicators.

The major causes of death in ATLL are opportunistic pulmonary infections and progressive disease, often in association with hypercalcemia (82-83).

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