

## Chapter

# 80

## *Chronic Lymphatic Leukemia— Current Management Strategy*

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### **CHRONIC LYMPHATIC LEUKEMIA (CLL)— CURRENT MANAGEMENT STRATEGY**

CLL is said to be the most common leukemia occurring in adults in the west, but in India and other Asian countries it is much less common. It is a low grade malignancy arising from a single clone of B lymphocytes and is characterized by accumulation of small mature looking B lymphocytes in blood, bone marrow, and lymphoid tissues. It is an interesting clinical problem with totally asymptomatic patients on one side to those presenting with multiple lymph node enlargement and or hepatosplenomegaly on the other side. There is an apparent lack of interest among some Hematologists and Oncologists in our country, probably due to the age of the patients, lower incidence and narrow therapeutic options.

#### **Etiology**

The cause of the disease is unknown but must be due to errors in the lifestyle, diet and environment of the patients. Infections, toxins, pesticides, radiation, genetic predisposition all have been implicated without any definite proof.

#### **Pathology**

Most cases of CLL are B-lymphocyte type (95% or more), though rarely T-lymphocytes may be involved. The monoclonal population of B cells expresses pan B-cell antigens CD19, CD20, CD23 and CD 24 and has low expression of monoclonal surface immunoglobulin of IgM ± IgD of a single κ or λ light chain In 95% of cases these cells co-express CD5 also which is a pan T cell antigen. These tumor cells do not usually secrete immunoglobulins except in 5% of case when they secrete a paraprotein similar to that on their surface.

Monoclonality of the cells can be demonstrated by the monoclonal surface immunoglobulins, evidence of immunoglobulin gene rearrangements and rarely by the monoclonal paraprotein in serum if they secrete it. The cells have a low proliferation rate except in advanced stages. The organomegaly is due to infiltration by the malignant clone the B cells in the concerned areas. Enlarged lymph nodes histologically resemble diffuse well-differentiated lymphoma. Liver, spleen and bone marrow show infiltration by the abnormal clone of lymphocytes. Progressive replacement of the normal bone marrow can finally lead to bone marrow failure and consequent neutropenia, anemia and thrombocytopenia. Lymphocytes may infiltrate other organs and the skin as well. The T cell function is abnormal and has a blunted response to T cells mitogens and show a decreased delayed hypersensitivity reaction to recall antigens. Immune status of the host is defective due to hypogammaglobulinemia and defective T cell function. Autoantibodies are often produced by non-neoplastic B cells suggesting a dysregulation in immune tolerance to self antigens. They can develop autoimmune hemolytic anemia(AIHA), Immune thrombocytopenia, neutropenia and even pure red cell aplasia (PRA) due to auto-antibodies.

#### **Clinical Features**

The disease affects adults, usually above 50 years and the risk increases progressively as age advances, and is 2-3 times higher in older men as compared to older women and is extremely rare in younger individuals. Most patients are asymptomatic or they present with nonspecific symptoms like fatigue, tiredness and vague ill health. Very often the diagnosis is suspected on a routine physical examination which most commonly detects lymphadenopathy with or without

splenomegaly or blood examination in apparently asymptomatic subjects. In about 80% of cases, the disease presents with painless lymphadenopathy usually in neck axillae and inguinal regions but can occur at other sites as well. The nodes can be small, moderate or large in size causing even disfigurement. Tonsils also may be enlarged considerably producing even upper airway obstruction. Large lymph nodes in the abdomen can present with lower limb edema due to IVC compression. Retroperitoneal nodes can produce ureter obstruction and perportal nodes can produce biliary obstruction.

Enlargement of the liver or spleen is less common at diagnosis, but around 40% have mild to moderate splenomegaly and in 10% splenomegaly may be the only sign in the absence of lymphadenopathy. Sometimes splenomegaly can lead on to hypersplenism and pancytopenia. But in general cytopenia in CLL is more often due to marrow infiltration or autoimmune process. Anemia in CLL can be due to marrow infiltration (by lymphocytes replacing the erythroid series), autoimmune hemolysis, hypersplenism, Pure red cell aplasia or incidental nutritional deficiency of B<sub>12</sub> or folate or myelosuppressive effect of chemotherapy or even iron deficiency. Considering the age group of the patients affected, they may sometimes present with exacerbation of another preexisting illness like CVA, IHD or COPD.

Some patients have an exaggerated cutaneous response to mosquito bites. Recurrent infections of the respiratory and urinary tracts may occur due to the immunodeficiency due to decreased production of IgG, IgA and IgM and poor T cell function. Hepatomegaly due to leukemia cell infiltration is not common. But leukemic infiltrates can occur in any area including liver, kidneys, retroorbital area, scalp, prostate, pharynx, lung, GIT, pleura or CNS- the manifestations vary depending on the site and extent of infiltration by the leukemic cells.

### Laboratory Investigations

Diagnostic finding in peripheral blood is the sustained monoclonal lymphocytic leukocytosis more than 5000/cmm but often in the range of 25,000-200,000/cmm ( $25-200 \times 10^9/L$ ). When the counts are in the range of 800,000/cmm it can be associated with hyper viscosity and leukostasis. The cells are morphologically similar to mature lymphocytes. Direct Coomb's test can be positive in those with hemolysis due to IgG anti red cell auto antibodies. Thrombocytopenia can be due to tumor infiltration of marrow, hypersplenism or autoimmune thrombocytopenia.

Extensive marrow infiltration occurs in the advanced stages of the disease. Lymph nodes are also infiltrated

by the same type of lymphocytes and the histology may resemble low grade small lymphocytic lymphoma. Hypogammaglobulinemia is usually seen on electrophoresis but 5% can have monoclonal paraprotein of IgG type or, even rarely, IgM paraprotein can occur causing confusion to differentiate from Waldenstrom macroglobulinemia. Flow cytometry helps in differentiating CLL from Lymphoma and to identify the monoclonality and the B cell origin. CLL cells are typically CD5+, CD10-ve, CD19+, CD23+, CD103-ve and CD20 (dull). Low level expression of CD 20 is a hall mark of CLL cells which helps to differentiate from other B cell malignancies. Pseudohyperkalemia can occur due to severe leukocytosis.

### *Differential Diagnosis Includes Other B Cell Neoplasms and Infections*

1. Other causes of lymphocytosis like some viral and bacterial infections – the lymphocytosis in such infections is not persistent, the patients are younger, the clinical setting is different and the cells are not monoclonal.
2. Low grade small lymphocytic B cell lymphoma; the lymph node histology is similar and even the surface antigens are almost the same, so the distinction is basically made by clinical evaluation. CLL is associated almost always with blood lymphocytosis and marrow lymphocytosis with or without lymphadenopathy. Whereas in lymphoma it is primarily associated with lymphadenopathy but marrow and blood lymphocytosis is uncommon.
3. Mantle cell lymphoma – The B cells are almost similar with even same surface antigens but there is less of blood and marrow lymphocytosis and the B cells do not express CD23; the histology of involved lymph nodes is often different - it shows reactive germinal centers surrounded by well defined expanded mantle zones of monoclonal B cells, in contrast to the diffuse involvement in CLL.
4. Splenic marginal zone lymphoma – another B cell neoplasm which present with marked splenomegaly often have moderate lymphocytosis but not as high as in CLL; the monoclonal B lymphocytes appear as atypical villous lymphocytes and they do not express CD23. Splenic infiltrate in this disorder shows a readily identifiable marginal (peripheral) zone of larger lymphocytes with an inner zone of small lymphocytes within the white pulp of spleen. In CLL there is diffuse involvement of white pulp and do not have a readily identifiable marginal zone.
5. Prolymphocytic Leukemia closely mimics CLL but the B cells here are larger, morphologically different

and have low expression of CD5 and have high levels of surface immunoglobulins.

6. Hairy cell leukemia presents with massive splenomegaly and less of peripheral blood and marrow lymphocytosis. The B cells in this disorder can be differentiated by the larger size and the electron microscopic hairy projections on the cells. These cells are strongly positive for tartrate-resistant isozyme 5 of acid phosphatase activity (TRAP)
7. Waldenstrom macroglobulinemia can also be confused sometimes when the CLL cells secrete paraproteins. In Waldenstroms the B cells are plasmacytoid lymphocytes, they are always present in marrow and sometimes in blood also, but are morphologically different. Distinguished from CLL by morphology and expression of CD10 (CALLA).
8. T cell lymphoproliferative disorders: A heterogeneous group, including T cell CLL and T cell prolymphocytic leukemia are to be differentiated sometimes from B cell CLL. They are uncommon malignancies and have different clinical presentations and morphological differences are often present and the cells lack CD19 and CD20 which are B cell restricted antigens.

## MANAGEMENT OF CLL

Life expectancy after diagnosis varies widely and therefore a clinical staging is used since it correlates with the response to treatment and survival.

### Staging of Chronic Lymphatic Leukemia (Rai 1975)

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| <b>Stage 0</b>   | Blood and marrow lymphocytosis only. No enlargement of lymph nodes, spleen or liver. Hemoglobin is above 11 gm/dL and platelet count is over $100 \times 10^9/L$ |
| <b>Stage I</b>   | Lymphocytosis + enlarged lymph nodes + other features as in stage 0  |
| <b>Stage II</b>  | Lymphocytosis + enlarged spleen, liver or both. Lymph nodes may or may not be enlarged   |
| <b>Stage III</b> | Features as in stage II but with hemoglobin is less than 11 g/dL   |
| <b>Stage IV</b>  | Features as in stage II or III, but with platelet count below $100 \times 10^3/cmm$  |

The disease follows a slow and progressive course, remaining asymptomatic for several years, and ultimately ending fatally because of infection, bone marrow failure, or transformation to an aggressive histology like Prolymphocytic Leukemia or lymphoma. In general, patients with stages 0 has a very low risk

and survive more than 150 months, whereas those with intermediate risk (stage II and III) survive for 90 months. High risk (Stage III and IV) patients survive only for around 20 months. Most of our patients at diagnosis are in intermediate or high grade stage. CLL can transform to an aggressive large B cell high grade lymphoma at any point in the course of the disease and is called *Richter's syndrome*. Though terminal blast transformation can occur it is very rare as compared to, chronic myeloid leukemia.

In 1981, Binet suggested an alternate three stage classification considering total lymphoid mass. Stage A having less than three areas of lymphoid enlargement, Stage B having three or more areas of lymphoid enlargement. The advanced form of stage C includes all patients having anemia and thrombocytopenia. Those patients with a leukemic cell doubling time less than 12 months also have a shorter survival.

Worse prognosis is also suggested by CD38 expression on the leukemic cells and in those with abnormal cytogenetic markers like Trisomy 12, or abnormalities in Chromosome 14 or 6. Marrow biopsy showing a diffuse pattern of infiltration by leukemic cells also correlates with a worse prognosis.

## Indications for Starting Therapy in CLL

1. Advanced stage of the disease (Stage III and IV of Rai or stage C of Binet)
2. Anemia or Thrombocytopenia indicating diffuse bone marrow infiltration
3. Disfiguring or site threatening lymph node enlargement
4. Disease related symptoms
5. Markedly enlarged or painful spleen
6. Blood lymphocyte doubling time less than 6 months,
7. Prolymphocyte transformation
8. Richter transformation.
9. Autoimmune thrombocytopenia or hemolysis

In newly diagnosed patients if they do not have any of the above mentioned indications they should be kept under regular follow-up for several months with the following action plans

1. Regular monitoring of blood counts to assess the lymphocyte doubling time
2. Look for the development of anemia and thrombocytopenia
3. If they remain stable without rising counts the follow-up frequency can be reduced to once in 3 or 6 months.

On the other hand, once a decision to treat has been taken the baseline objectives should be defined and one should discontinue the treatment on resolution of the original reasons for initiating treatment. Although it is customary in the west to withhold treatment till the disease reaches stages III or IV, in Indian subjects treatment may have to be started earlier as in many patients therapy offers significant benefit and prolonged survival.

### *Evaluating Response to Therapy*

Basically assessed by clinical and hematological parameters, complete response is characterized by:

- Free of the clinical problems for which we have initiated treatment.
- No constitutional symptoms, no organomegaly.
- Normal blood counts and Hb >11 g without transfusion.
- Marrow containing < 30% lymphocytes and no lymphocyte nodules.

In case patient shows complete response one can look for minimal residual disease (MRD) by PCR for Ig gene rearrangement of the leukemia clone) Those without MRD have a longer survival

Progressive disease is characterized by any of the following:

- 50% increase in lymphocyte count.
- Transformation to aggressive histology.
- Increase in spleen and lymph node size.
- Appearance of new lymph nodes.

## **Treatment**

### *Deoxy-adenosine Analogues*

Fludarabine given as a single agent appears to be the most suitable drug but it is expensive. It is given in a dose of 25 mg/m<sup>2</sup> body surface area IV daily as a 30 minute infusion for 5 days every 28 days. It is effective in bringing about higher response rates and longer remissions especially when used as frontline therapy. Patients in advanced stage, prior therapy and those with low albumin levels show a poorer response. Those who do not show response to first two cycles are unlikely to respond and hence to be given another form of therapy. An oral form of the drug with equal efficacy is being developed. Whether it improves overall survival is still not certain. Side effects include neutropenia, reversible

neurotoxicity, tumor lysis, immunosuppression and new onset autoimmune diseases but there is no increase in second malignancies.

*Cladribine* is another drug of the same class as Fludarabine with almost equal but not superior efficacy. Monthly cycles are given as an IV infusion over 2 hours at a dose of 0.12 mg/kg /day for 5 consecutive days.

*Pentostatin* is a purine analogue structurally related to adenosine and has been found to have improved response rates. Dose: 2mg/m<sup>2</sup> /day for 5 days every 28 days; dosage increased or reduced by 0.5 mg/m<sup>2</sup> depending on disease response or hematologic toxicity.

### *Alkylating Agents*

Chlorambucil (*Leukeran/Clokeran*) is still the main drug in chemotherapy for advanced stage. As it does not appear to improve survival it should not be used in asymptomatic patients with early stage disease. It is started usually with 2 to 4 mg per day continuously till the total leukocyte count becomes normal and the lesions disappear. An alternate dosage schedule is 0.4 mg/Kg/body weight of total dose divided into 4 equal doses and given on days 1 through 4. This cycle can be repeated every two to 4 weeks. It is generally a well tolerated drug. Pulse therapy with chlorambucil is less myelotoxic

Cyclophosphamide 50-100 mg/day can be used instead of chlorambucil. It can also be given in pulses of 500-750 mg/m<sup>2</sup> IV every 3-4 weeks. It is as effective as chlorambucil.

Corticosteroids, are useful as single agents in patients with autoimmune hemolytic anemia and immune thrombocytopenia, of CLL but is also useful for control of CLL. Given in cycles along with alkylating agents steroid enhances the effect of alkylating agents.

Combination chemotherapy has been beneficial in resistant cases. The usual combination is cyclophosphamide, doxorubicin, vincristine and prednisolone.

Alemtuzumab, a monoclonal antibody against CD52, is occasionally used in patients refractory to commonly used drugs. This drug can bind to the surface protein on CLL B cells and can mediate antibody-mediated cellular cytotoxicity.

The standard treatment for advanced CLL is always as combination therapy with Chlorambucil and prednisolone. Cycles of Chlorambucil 0.5 to 0.7mg/Kg on day 1 and Prednisolone at 80mg/day for days 1 to 5. This course is repeated at every 2 to 4 weeks. The total dose of Chlorambucil can be given in divided doses also. The dose can be increased or reduced depending on disease response and myelosuppression. Rituximab, a

monoclonal antibody specific for CD 20 is also found to be effective though CD20 expression is weak on CLL cells.

Combination of Fludarabine and monoclonal antibodies may be another option barring the prohibitive cost.

Combination of Fludarabine and cyclophosphamide could be useful in patients who are non responsive to other agents. Fludarabine 25 mg/m<sup>2</sup> day for 3 days and Cyclophosphamide 250 mg/m<sup>2</sup>/day for 3 days given every 28 days.

Fludarabine/Cyclophosphamide/ Rituximab is another combination which is probably the most superior.

Fludarabine/prednisolone combination or Fludarabine + chlorambucil combination were not shown to be superior to any other regime and hence not recommended.

Optimal improvement occurs in 1-2 years, though the neoplasm is not eradicated.

Infective episodes demand prompt treatment with antibiotics. Immunoglobulin can be given prophylactically in doses of 50-100 mg/Kg periodically to reduce the frequency and severity of bacterial infections, again the cost is prohibitive.

Splenectomy can be beneficial in those patients with cytopenia, especially thrombocytopenia, due to hypersplenism.

Radiotherapy is useful in bulky lymph nodes compromising nerves or other organs. Splenic irradiation is useful in massive splenomegaly with severe pain in poor candidates for splenectomy, when it is indicated.

Leukapheresis has been found to be beneficial in some patients in removing the leukemic cells and thereby reducing the tumor load and also to reduce leukostasis.

Several experimental therapies are under evaluation. Autologous stem cell transplantation, was found only to prolong survival but no cure, probably because the stem cell collections were contaminated with CLL cells. Younger patients with poor prognosis may be good candidates for allogenic stem cell transplantation.

Supportive therapy with platelet transfusion may be required sometimes when they have active bleeding due to severe thrombocytopenia which may develop due to disease or therapy. Severe anemia may require packed cell transfusion preferably leukocyte depleted.

Erythropoietin may be used to reduce transfusion requirements.

*Infections in CLL:* They are susceptible to recurrent infections in the lungs, skin or urinary tracts by organisms like *S. pneumoniae*, *S. aureus*, *E.coli*, Varicella virus etc. Active disease, prior therapy and hypogammaglobulinemia, are major risk factors for infections.

### Prolymphocytic Leukemia

B cell prolymphocytic leukemia is a rare variant of CLL, seen in males above the age of 60 years and showing gross splenomegaly and a very high white cell count, often above 400 × 10<sup>9</sup>/L. Lymphadenopathy is rare. The characteristic cell is the large lymphocyte showing a prominent nucleolus. The course is rapidly downhill and prognosis is poor.

### Hairy Cell Leukemia

This is a variant of chronic lymphatic leukemia and is rare. It is seen in the age group 40-80 years and males are affected four times more common than females. Patients present with massive splenomegaly, anemia, relative lymphocytosis, more often with a low total leukocyte count, often pancytopenia is present. The B lymphocytes are larger than that in CLL and show the characteristic fine hairy projections which can be detected in peripheral smear and bone marrow, but best brought out by electron microscopy. The cytoplasm shows a number of villi which give the hairy appearance. The diagnostic histochemical test for hairy cells is acid phosphatase staining reaction resistant to the action of tartarate (TRAP). Bone marrow is infiltrated heavily and it is difficult to aspirate and often a dry tap is obtained. Marrow biopsy and imprint smears show the hairy cells.

### Treatment

In the early stages corticosteroids are useful. The disease responds best to splenectomy. Alpha interferon in a dose of 2 million units/m<sup>2</sup> given thrice a week is the treatment of choice. It is most probably only palliative. Treatment is given when the patient develops severe neutropenia. Pentostatin and Cladribine produce lasting remissions.

### Dose

*Pentostatin* - 4 mg/m<sup>2</sup>/week for three weeks, then once in 2 weeks for 6 weeks followed by once a month for 6 months, given intravenously.

*Cladribine*- 0.1 mg/Kg/bw by continuous IV infusion for 5 days every month.

### SUGGESTED READING

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