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CHRONIC LYMPHOCYTIC LEUKEMIA: A REVIEW

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1. INTRODUCTION

Chronic lymphocytic leukemia (CLL), is a typically slow-growing cancer which begins in lymphocytes in the bone marrow and extends into the blood. It is the proliferation and accumulation of lymphocytes (usually B cells) that are relatively unresponsive to antigenic stimuli. CLL is a disease predominantly of the older age group as the median age at initial diagnosis is 65-70 years and the male to female ratio 2:1.[1]

Chronic lymphocytic leukemia is the most frequent type of leukemia in western countries.[2] In the USA CLL estimated at 3.5 per 100,000 (male 5 female 2.5). in the UK estimate of 6.15 per 100,000 have been reported.[3]

2. Clinical Features

Chronic lymphocytic leukemia is diagnosed in an asymptomatic phase in 35 to 45 per cent of patients. In symptomatic patients the most common features are symmetrical lymph node enlargement in most of the patients and symptoms and signs of anemia. An important complication in approximately 10% of cases is acquired hemolytic anemia. This is sometimes the first manifestation of chronic lymphatic leukemia. It should be suspected when the degree of anemia is in appropriately severe for the degree of lymph node and splenic enlargement, the degree of lymphocytosis, or when spherocytes or agglutination are present in the blood film.[4] A distinctive feature of the natural history of CLL is that neoplastic B lymphocytes accumulate over time. Therefore in all patients the occasional features are splenomegaly, hepatomegaly and hemorrhagic manifestation in patients with thrombocytopenia. The causes of thrombocytopenia are like ITP. This type of thrombocytopenia is respond to corticosteroid or splenectomy. Impaired platelet production due to hemopoietic tissue replacement by the diseases or from myelosuppressive effects of agents used for therapy of the disorder. Other

manifestations like respiratory infections, skin infiltration, tonsillar enlargement, nervous system manifestations, Bone or Joint pain and disturbance of vision or hearing are late manifestations[5]

3. Blood Picture

Hemoglobin is normal in early stages to moderate or severely depressed values in advanced CLL. Anemia is usually normochromic and normocytic. When anemia is due to hemolysis, it usually has the typical features of autoantibody-mediated red cell destruction, with spherocytosis, a positive Coomb's test and a reticulocytosis. The typical features of CLL are leukocytosis, with lymphocytes count ranged from 50,000 to 200,000/μ. Sometimes leukocytes are less than 10,000. 90% or more of the leukocytes are mature lymphocytes: Lymphocytes are usually seen as:

(i) Small cells with densely clumped nuclear chromatin and a narrow rim of cytoplasm (predominant)

(ii) Larger cells with lighter cytoplasm

(iii) Smear or "basket" cells –bare lymphocyte nuclei

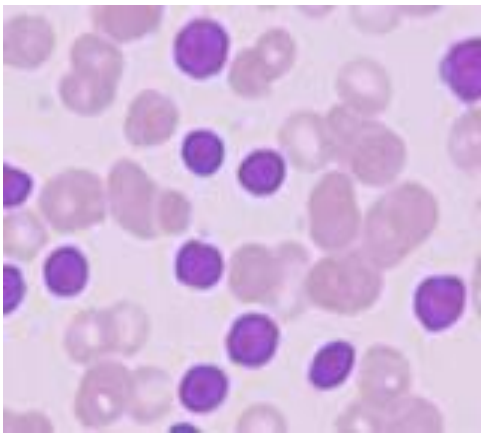

Figure: 1 Chronic lymphocytic leukemia

Thrombocytopenia, with counts less than 50,000/μL is common. It is a feature of advanced stage. Serum Immunogbulin decreased in most CLL in late stages. It may fall to 0.3 to 0.4 g/dl and patient become more susceptible to all types of infection.[4]

Richter syndrome (RS) is defined as the transformation of chronic lymphocytic leukemia (CLL) into an aggressive lymphoma, most commonly diffuse large B-cell lymphoma (DLBCL). RS occurs in approximately 2% to 10% of CLL patients during the course of their disease, with a transformation rate of 0.5% to 1% per year.[6]

4. Bone Marrow Aspiration and Biopsy

Usually are not necessary for making the diagnosis of CLL except in those aleukemic or subleukemic cases with no nodal or splenic involvement and few or no abnormal cells in the peripheral blood.

In marrow there is increase of lymphocytes and a corresponding reduction of megakaryocytes, myeloid precursors, and erythroid precursors. A bone marrow is only performed to assess marrow reserves and genetic analysis prior to therapy, and after treatment completion to assess response.

Chromosomal abnormalities are detected in more than 50% of patients with CLL and indicate a worse prognosis. The most frequently encountered is trisomy 12 (+ 12). Other cytogenetic abnormalities are 14q translocation.

In more than 90% of the cases, CLL lymphocytes express the CD5 antigen, which was formerly thought to be a T-cell antigen. Cells from most cases of B-CLL also expresses CD19, CD24, CD37 and CD21 antigen. About 60% of CLL are positive for CD23 but infrequently demonstrate positivity for CD22.[7]

Important molecular markers include ZAP70 and IgVH gene rearrangements. ZAP-70 is an intracellular protein that promulgates activation signals delivered to T lymphocytes and natural killer cells by their surface receptors for antigen.[8] It is rarely present in normal B cells but has been found in B cells from patients with CLL[9] Patients with clones having few or no V-gene mutations or with many CD38+ or ZAP-70+ B cells had an aggressive, usually fatal course, whereas patients with mutated clones or few CD38+ or ZAP-70+ B cells had an indolent course.[10]

The median survival of patients with chronic lymphocytic leukemia was about nine years. Clinical stages, blood lymphocyte counts and morphology, bone marrow histopathological findings, serum lactate dehydrogenase, immunophenotyping and cytogenetic abnormalities are good predictors of survival.[11-15] Table 1.

Table 1: The RAI staging for chronic lymphocytic leukemia[11]

Stages	Characteristics	Survival
0	Peripheral blood lymphocytosis >15000/μL	>150 months
I	Lymphocytosis and lymphadenopathy Hepatomegaly or splenomegaly or both	100 months
II	Anemia (<11g/dl or Hct <33%)	71 months
III	Thrombocytopenia (platelets <	19 months
IV	100,000/μL	19 months
Adapted from Rai KR, et al, Clinical staging of chronic Lymphocytic leukemia. Blood 1975; 46:219		

5. Treatment of Chronic Lymphoyctic Leukemia

The CLL patients are staged according to Rai staging system. Most patients are managed supportively. Asymptomatic patient and those with early stages (0,I, II) may not be treated. 2/3 of patients respond to therapy with a single alkylating agent such as chlorambucil which may be used (20-30 mg/m^2 orally every 2-4 weeks; or in a daily dose of 2-5 mg/m^2 until WBCs stabilized. Patients with stage III and IV are treated with chlorambucil combined with prednisone (20-40mg/m^2/d) for one week every 2-3 weeks.

Prednisolone is effective in the treatment of autoimmune hemolysis or thrombocytopenia.[16]
Purine Nucleoside Analogus: (E.g deoxycoformycin, 2-chlorodeoxy-adenosine, fludarabin) based on analogues of adenosine have recently become available for the treatment of CLL and low grade lymphomas. Fludarabine may be more effective as a single agent than chlorambucil. Fludarabine also useful in patients resist to chlorambucil (25-30 mg/m^2/day i.v for 45 days) repeated each month for 3-6 months.[17]

Alternatively, they may be given CVP regimen (or R-CVP) every 3 weeks:
Rituximab IV 375mg/m2 day 1, Cyclophosphamide IV 750 mg/m2 day 1

Vincristine IV 1.4 mg/m2 (dose at 2 mg) day 1, Prednisone PO 100 mg, orally days 1-5. (if rituximab not available, give CVP at the same doses).

Current therapies of CLL include purine analogues (fludarabine and cladribine), monoclonal antibodies against CD20 (rituximab) and CD52 (alemtuzumab), radiation and alkylating agents (chlorambucil and cyclophosphamide). FCR (Rituximab 375 mg/m² IV day 1, Fludarabine 25 mg/m² IV days 2–4, Cyclophosphamide 250 mg/m² IV over 1 hour days 2–4) have shown response rate of 30% to 60% in fludarabin-pretreated populations.[18-19]

Alemtuzumab is showing increasing promise as a single or combined agent in refractory disease.

Standard Bendamustine-Rituximab regimen; is Bendamustine IV 90 mg/m2 on days 1,2 and Rituximab IV 375 mg/m2 on day 1 are administered every 4 weeks for 4 cycles.

Ibrutinib (Imbruvica) is a targeted drug that can be used to treat chronic lymphocytic leukemia (CLL). It is a bruton tyrosine kinase (BTK), is a critical enzyme in the B-cell receptor signaling pathway and is a novel therapeutic target in CLL approved for the treatment of patients with relapsed refractory chronic lymphocytic leukemia (RR-CLL).[20-21]

Idelalisib (Zydelig) is another targeted drug for CLL. It blocks a kinase protein called PI3K. This drug has been shown to help treat CLL after other treatments have been tried. The combination of idelalisib and rituximab, as compared with placebo and rituximab, significantly improved progression-free survival, response rate and overall survival among patients with relapsed CLL who were less able to undergo chemotherapy.[22]

Venetoclax (Venclexta) is a selective drug that targets BCL-2, a protein in CLL cells had a manageable safety profile and induced substantial responses in patients with relapsed CLL or small lymphocytic lymphoma (SLL), including those with poor prognostic features.[23]

Autologous and allogenic bone marrow transplantations are being explored as treatment options and promising treatment modalities.[24]

Outcomes are improved by the addition of immunotherapy to combination chemotherapy for initial treatment in all subsets of treated patients.

Overall response rates between 75% and 90% and complete responses between 22% and 45% are expected in the current era, with more than 80% of treated patients alive at 3 years. Overall, 5-year survival has increased to 66% from 60% ($P < .001$) in the past 10 years.[25]

6. Other Measures

Immunoglobulin replacement: e.g. 250-mg/kg month by intravenous infusion is useful for patients who have hypogammaglobulinemia and/ or recurrent infections and a poor IgG immune response to pneumococcal polysaccharide vaccination.[26]

Prophylaxis against pneumocystis, hepes simplex virus, and varizella zoster virus, as well as a monitoring for CMV reactivation should be considered when treating CLL patients with these agents.[27]

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