Annals of Oncology 16 (Supplement 1): i50–i51, 2005
doi:10.1093/annonc/mdi806

ESMO Minimum Clinical Recommendations for diagnosis, treatment and follow-up of chronic lymphocytic leukemia

Incidence

- B-chronic lymphocytic leukemia (B-CLL) has an incidence of 3/100 000 per year in the western hemisphere. The incidence is increasing up to almost 50/100 000 per year after the age of 70 years. The incidence was reported to increase in younger patients, with about one-third of B-CLL patients younger than 55 years old. However, this trend does not seem to have changed the overall incidence of B-CLL so far. B-CLL represents the most frequent non-Hodgkin's lymphoma (11%) and leukemia of adults (25%).

Diagnosis

- The diagnosis of B-CLL is established by the following criteria:

  Sustained increase of peripheral blood lymphocytes $\geq 5 \times 10^9$ cells/l not explained by other clinical disorders.

  Predominance of small, morphologically mature lymphocytes in the blood smear.

  Immunophenotyping: The composite immunophenotype CD5+, CD23+, CD20 dim+, sIg dim+, FMC7− allows one to distinguish most cases of B-CLL from other CD5+ B-cell lymphoma. The Matutes score may be helpful in this regard.

  Lymph node biopsy: Histological confirmation is recommended whenever an enlarged, accessible, peripheral lymph node allows the procedure without additional risk.

  The following additional examinations are recommended for the *initial* evaluation *[V, D]*:

  Physical examination including a careful palpation of all lymph node areas.

  LDH, β2-microglobulin, bilirubin, serum–protein electrophoresis, Coombs test.

  Chest X-ray, abdominal ultrasound or computer tomography.
- FISH is becoming increasingly used for risk stratification and for choosing the treatment of choice in selected younger high risk patients.
- For prognostic and therapeutic reasons, every effort should be made for adequate differential diagnosis against mantle cell lymphoma using morphology, immunophenotyping and fluorescence *in situ* hybridization and/or molecular biology for detection of (t11;14) translocation and staining for cyclin D1.

Staging and prognosis

- The median survival at diagnosis varies between 2 and >10 years according to the initial stage of the disease. Two clinical staging systems are used. In Europe, the Binet staging system is generally more accepted. It separates three groups of different prognosis (Table 1).

Treatment of early disease

- (Binet stage A and B without symptoms; Rai 0, I and II without symptoms.)
- The standard treatment of patients with early disease is a watch and wait strategy with controls of blood cell counts and clinical examinations every three months *[I, A]*. Patients with rapid disease progression (lymphocyte doubling time <12 months) should be treated as below.

Treatment of advanced disease

- (Binet stage A and B with symptoms, Binet stage C; Rai II with symptoms, Rai III–IV.)
- B-symptoms, cytopenias not caused by autoimmune phenomena and symptoms or complications from lymphadenopathy, splenomegaly or hepatomegaly are indications for chemotherapy *[I, A]*.
- Options are purine analogues (fludarabine, cladribine) or chlorambucil. Randomized trials have not demonstrated a survival benefit for either option so far *[I, A]*.
- In younger patients (≤65 years, physically active, no major health problems) purine analogues may be recommended as initial treatment, because they achieve a higher rate of complete remissions and a longer progression- and treatment-free survival than chlorambucil. The risks and benefits of fludarabine are better documented than those of other purine analogues. Combinations of purine analogues with other drugs, in particular cyclophosphamide appear to result in a higher complete remission rate than single agent therapy, but with a higher toxicity.
- In older patients (>65 years, with high comorbidity) chlorambucil can be given as first line therapy, because it is less myelotoxic and immunosuppressive than purine analogues thus resulting in fewer infections.

Second-line chemotherapy

- The first line treatment may be repeated, if the relapse or progression occurs >6 months after the initial therapy *[V, D]*.
- If the relapse occurs within 6 months or if the disease does not respond to the first line therapy, the following options are recommended *[V, D]*:

Table 1. Prognostic stages of CLL

		Frequency (%)	Median survival
Binet stage:			
A		63	>10 years
B		30	5 years
C		7	1.53 years
Rai stage:			
0	Low	30	>10 years
I II	Intermediate	60	7 years
III IV	High	10	1.5 years

- Fludarabine after chlorambucil.
- Fludarabine combinations (with cyclophosphamide and / or mitoxantrone (FCM) in fludarabine refractory patients.
- Monoclonal antibody (alemtuzumab) in chemotherapy refractory patients.
- High dose therapy followed by autologous or allogeneic progenitor cell transplantation remains investigational.

Response evaluation

- Response evaluation includes a blood cell count and a marrow biopsy (only in patients with complete hematologic remission), as well as a chest X-ray and an abdominal ultrasound or computer tomography *[V, D]*.

Follow-up

- Follow up of asymptomatic patients should include a blood cell count every 3 months, as well as a regular examinations of lymph nodes, liver and spleen. Special attention should be given to the number of atypical lymphocytes in particular to prolymphocytes *[V, D]*.

Note

Levels of Evidence *[I–V]* and Grades of Recommendation *[A–D]* as used by the American Society of Clinical Oncology are given in square brackets. Statements without grading were considered justified standard clinical practice by the experts and the ESMO faculty.

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Approved by the ESMO Guidelines Task Force: August 2003, last update December 2004.

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