Chronic lymphocytic leukemia: ESMO Clinical Recommendations for diagnosis, treatment and follow-up

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incidence

Chronic lymphocytic leukemia (CLL) has an incidence of 3–5/100 000/year in the western hemisphere. The incidence is increasing up to 50/100 000/year after the age of 70 years. Though the incidence has been reported to increase in younger patients, with about one-third of CLL patients younger than 55 years, the overall incidence of CLL has rather decreased during the past 15 years. CLL represents the most frequent leukemia of adults (25%).

diagnosis

The diagnosis of CLL is established by the following criteria:

- Sustained increase of peripheral blood lymphocytes ≥5 × 10⁹ cells/l not explained by other clinical disorders.
- Predominance of small, morphologically mature lymphocytes in the blood smear.
- Immunophenotyping: the composite immunophenotype CD5⁺, CD19⁺, CD20⁻ (low), CD23⁺, slg low, CD79b low, FMC7⁻ allows the distinction of most cases of B-cell type CLL from other CD5⁺ B-cell lymphoma.
- Bone marrow biopsy is not needed for diagnosis, but is recommended before initiating therapy, in order to evaluate unclear cytopenia.

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

- Physical examination including a careful palpation of all lymph node areas.
- LDH, bilirubin, serum protein electrophoresis, Coombs test.
- Chest X-ray.
- Because the detection of cytogenetic abnormalities by fluorescent in situ hybridization (FISH) has apparent prognostic value, this examination should be carried out during the initial evaluation of a patient with CLL.
- For prognostic and therapeutic reasons, every effort should be made for adequate differential diagnosis against mantle zone lymphoma using morphology, immunophenotyping and FISH and/or molecular biology for detection of (t11;14) translocation and staining for cyclin D1.
- Newer prognostic parameters such as the expression of CD38, ZAP70 and the immunoglobulin mutational status (IgVH mutation) may predict the time to progression from an early stage to advanced disease, but should not be used for a treatment indication in CLL. At present, their value should be further investigated in clinical trials.

staging and risk assessment

The median survival at diagnosis varies between 1 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.

Table 1. Prognostic stages of CLL

<table>
<thead>
<tr>
<th>Binet stage</th>
<th>Frequency (%)</th>
<th>Median survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>63</td>
<td>&gt;10 years</td>
</tr>
<tr>
<td>B</td>
<td>30</td>
<td>5 years</td>
</tr>
<tr>
<td>C</td>
<td>7</td>
<td>1.5–3 years</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Rai stage</th>
<th>Frequency (%)</th>
<th>Median survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 low</td>
<td>30</td>
<td>&gt;10 years</td>
</tr>
<tr>
<td>I/II intermediate</td>
<td>60</td>
<td>7 years</td>
</tr>
<tr>
<td>III/IV high</td>
<td>10</td>
<td>1.5 years</td>
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</tbody>
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Conflict of interest: Dr. Eichhorst has reported that she is currently conducting research sponsored by Roche and Mundipharma and that she is member of the speakers’ bureau of Schering. Prof. Hallek has reported that he is currently conducting research sponsored by Roche and Mundipharma.
The standard treatment of patients with early disease is a watch and wait strategy with controls of blood cell counts and clinical examinations every 3 months [I, A]. Patients with active disease as defined by rapid disease progression (e.g. lymphocyte doubling time <6 months) should be treated as patients with advanced disease.

**treatment of advanced disease**

Binet stage A and B with symptoms, Binet stage C; Rai II with symptoms, Rai III–IV.

Significant B symptoms, cytopenias not caused by autoimmune phenomena and symptoms or complications from lymphadenopathy, splenomegaly or hepatomegaly as well as autoimmune anemia and/or thrombocytopenia poorly responsive to corticosteroid therapy are indications for chemotherapy [I, A].

Options are purine analogs (fludarabine, cladribine) alone or in combination with cyclophosphamide or chlorambucil. Randomized trials have not demonstrated a survival benefit for either option so far [I, A].

In physically fit patients (physically active, no major health problems) the combination of fludarabine and cyclophosphamide (FC) is currently recommended as initial treatment, because this combination induces a higher rate of complete remission and longer progression- and treatment-free survival than chlorambucil or purine analog monotherapy [I, A]. The combination of cladribine plus cyclophosphamide has not produced significantly longer progression-free survival (PFS) than cladribine alone. The addition of monoclonal antibodies such as rituximab (R) or alemtuzumab (A) to purine analog-based treatment regimens results in very high and qualitatively better remission, but a benefit in PFS is currently being tested in randomized trials [III, B].

In patients with relevant co-morbidity (in particular renal insufficiency) chlorambucil or a dose-reduced fludarabine monotherapy can be given as first-line therapy, because they appear to be less myelotoxic than the FC combination.

Patients showing the chromosomal defect del(17p) frequently do not respond to conventional chemotherapy with fludarabine or FC. These patients may be initially treated with alemtuzumab monotherapy or combination therapy. Allogeneic transplantation within clinical trials might be considered as first-line therapy in these patients.

**second-line chemotherapy**

The first line treatment may be repeated, if the relapse or progression occurs >12 months after initial therapy [V, D]. If relapse occurs within 12 months or if the disease does not respond to the first-line therapy, the following options are recommended in accordance with the administered first-line therapy [V, D]:

- Fludarabine, FC or cladribine after chlorambucil.
- Fludarabine combinations [with cyclophosphamide (FC) and/or mitoxantrone (FCM)] ± monoclonal antibodies (FR, FCR, FA) in fludarabine-refractory patients or relapse after fludarabine-based therapy.
- Monoclonal antibody (alemtuzumab), especially in chemotherapy-refractory patients.
- Bendamustine ± monoclonal antibodies after chlorambucil or purine analog-based therapy.
- High-dose therapy followed by autologous or allogeneic progenitor cell transplantation remains investigational.
- Allogeneic progenitor cell transplantation is the only curative therapy so far and is indicated in high-risk [del(17p), del(11q)] and/or refractory disease.

**response evaluation**

Response evaluation includes careful physical examination and a blood cell count. A marrow biopsy is only necessary in patients with complete hematologic remission and in clinical trials. Chest X-ray and an abdominal ultrasound or computed tomography for response evaluation can be considered for response evaluation, if abnormal before therapy [V, D].

**follow-up**

Follow up of asymptomatic patients should include a blood cell count every three months, as well as a regular examinations of lymph nodes, liver and spleen. Special attention should be paid to the appearance of autoimmune cytopenias (autoimmune hemolytic anemia, autoimmune thrombocytopenia) that occur in 10–15% of CLL patients [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.

**literature**

