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

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incidence

Chronic lymphocytic leukemia (CLL) has an incidence of 4/100 000/year in the western hemisphere. The incidence is increasing up to 50/100 000/year after the age of 70 years, but only 11% of CLL patients are younger than 55 years. CLL represents the most frequent leukemia of adults (25%).

diagnosis

The diagnosis of CLL is established by a sustained increase of peripheral CD5⁺ B-lymphocytes (≥5 × 10⁹ cells/l) not explained by other clinical disorders and a predominance of small, morphologically mature lymphocytes in the blood smear. The composite immunophenotype CD5⁺, CD19⁺, CD20⁺ (low), CD23⁺, slg low, CD79b low, FMC7⁻ allows most cases of CLL to be distinguished from other CD5⁺ B-cell lymphoma.

For prognostic and therapeutic reasons, every effort should be made for adequate differential diagnosis to exclude mantle cell lymphoma, splenic marginal zone lymphoma etc. by applying morphology, immunophenotyping and FISH and/or molecular biology for detection of t(11;14) translocation. In cases with isolated rapid tumor growth, biopsy should be performed to exclude Richter’s syndrome.

The following examinations are recommended prior to treatment initiation [III, B]: history and physical examination, including a careful palpation of all lymph node areas; complete and differential blood count; serum chemistry, including lactate dehydrogenase (LDH), bilirubin, serum immunoglobulin; Coombs’ test; chest X-ray; and infectious disease status, especially viral hepatitis, CMV.

The following additional examinations prior to treatment are desirable [III, C]: bone marrow biopsy is not needed for diagnosis, but is recommended prior to initiating therapy in cases with cytopenia.

Because the detection of cytogenetic abnormalities by FISH has apparent prognostic and predictive value, this examination should be performed prior to therapy.

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. CT scans are recommended only in clinical trials to assume the treatment response [III, C].

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

This includes Binet stages A and B without symptoms, and Rai stages 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 3–6 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

This includes Binet stages A and B with symptoms, Binet stage C, Rai stages 0–II with symptoms, and Rai stages III–IV.

Only patients with 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 in need of chemotherapy [I, A].

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**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>1.53 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</td>
<td>Low</td>
<td>30</td>
</tr>
<tr>
<td>I</td>
<td>Intermediate</td>
<td>60</td>
</tr>
<tr>
<td>II</td>
<td>High</td>
<td>10</td>
</tr>
<tr>
<td>IV</td>
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Options include purine analogue (fludarabine, cladribine, pentostatin)-based combinations like fludarabine, cyclophosphamide plus rituximab (FCR) in physically fit patients or chlorambucil in co-morbid patients. 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 FCR is currently recommended as initial treatment, as it induces a higher rate of complete remissions and a longer progression- and treatment-free survival than chlorambucil, purine analogue monotherapy or fludarabine plus cyclophosphamide (FC) combination therapy [I, A].

In a randomized trial, FC versus FCR achieved a significantly prolonged progression-free survival in comparison to FC only.

In patients with relevant co-morbidity (in particular renal insufficiency) there is no clear standard. Chlorambucil, a dose-reduced fludarabine monotherapy or FC combination can be given as first line therapy [II, B].

Patients with del(17p) frequently do not respond to conventional chemotherapy with fludarabine or FC. These patients should be treated initially with alemtuzumab monotherapy or combination therapy [III, B]. Allogeneic transplantation might be considered as first-line therapy in these patients within clinical trials [III, B].

Especially for alemtuzumab-containing regimes, the increased frequency of opportunistic infections (*Pneumocystis carinii*, herpes, fungal infections, CMV reactivation) should be considered carefully and adequate measures for prophylaxis and surveillance should be taken.

**second-line chemotherapy**

First-line treatment may be repeated, if the relapse or progression occurs >12 months after the initial therapy [III, B].

If the relapse occurs within 12 months or if the disease did not respond to the first-line therapy, the following options are recommended, dependent on the administered first-line therapy [III, B]: fludarabine or FC or FCR after chlorambucil; fludarabine combinations [with cyclophosphamide (FC) and/or mitoxantrone (FCM) and/or monoclonal antibodies (FR, FCR, FA)] in fludarabine-refractory patients or relapse after fludarabine-monotherapy; monoclonal antibody (alemtuzumab), either alone or in combination with purine analogue in chemotherapy-refractory patients and patients with del(17p); bendamustine as monotherapy or combination therapy [with mitoxantrone (BM) and/or rituximab (BR, BMR)] after chlorambucil or purine analogue-based therapy.

High-dose therapy followed by autologous or allogeneic progenitor cell transplantation remains investigational. However, 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. While autologous HSCT does not seem to yield better results than modern immunotherapeutics, allogeneic HSCT potentially eradicates the disease but is hampered by substantial morbidity and age restriction [III, B].

**response evaluation**

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

**follow-up**

Follow-up of asymptomatic patients should include a blood cell count every 3–6 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 and disease transformation (Richter’s syndrome) as suggested by local rapid lymph node growth and /or elevated LDH [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**


