Chronic lymphocytic leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

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epidemiology

Chronic lymphocytic leukaemia (CLL) is the most common leukaemia in the western world with an incidence of 4:100 000/year. The incidence increases to >30:100 000/year at age >80 years. The median age at diagnosis is 69 years; 14% of CLL patients are younger than 55 years.

diagnosis

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

• The diagnosis of CLL requires the presence of ≥5000 B lymphocytes/µl in the peripheral blood for the duration of at least 3 months. The clonality of the circulating B lymphocytes needs to be confirmed by flow cytometry.

• The leukaemia cells found in the blood smear are characteristically small, mature lymphocytes with a narrow border of cytoplasm and a dense nucleus lacking discernable nucleoli and having partially aggregated chromatin.

CLL cells co-express the T-cell antigen CD5 and B-cell surface antigens CD19, CD20 and CD23. The levels of surface immunoglobulin, CD20 and CD79b are characteristically low compared with those found on normal B cells. Each clone of leukaemia cells is restricted to expression of either κ or λ immunoglobulin light chains.

In contrast, the leukaemia cells of mantle cell lymphoma, despite also expressing B-cell surface antigens and CD5, generally do not express CD23. Other lymphoma entities to be separated are marginal zone lymphoma and immunocytoma.

The definition of small lymphocytic lymphoma (SLL) requires the presence of lymphadenopathy and/or splenomegaly. The number of B lymphocytes in the peripheral blood should not exceed 5·10⁹/l. SLL cells show the same immunophenotype as CLL. The diagnosis of SLL should be confirmed by histopathological evaluation of a lymph node biopsy whenever possible.

The following examinations are recommended before treatment initiation [III, B]:

• history and physical examination including a careful palpation of all lymph node areas;
• complete blood count and differential count;
• serum chemistry including LDH, bilirubin, serum-immunoglobulin;
• direct antiglobulin test (DAT);
• infectious disease status including hepatitis B and C as well as CMV and HIV serology;
• chest X-ray;
• ultrasound of the abdomen.

The following additional examinations before treatment are desirable [III, B].

• Bone marrow biopsy is not required for diagnosis. A bone marrow biopsy is recommended before initiating myelosuppressive therapies and for the diagnostic evaluation of unclear cytopenias.

• The detection of cytogenetic abnormalities, in particular of a deletion of the short arm of chromosome 17 [del(17p)] by fluorescent in situ hybridization (FISH) has therapeutic consequences. Therefore, a FISH analysis is recommended before the start of therapy.

• CT scans are recommended for baseline and final assessment in clinical trials [III, C], but not as routine practice outside of clinical trials.

staging and risk assessment

The median survival at diagnosis varies between 1 and >10 years. Two clinical staging systems are used. In Europe, the Binet staging system is more widely used. It separates three groups of different prognosis (Table 1). With the new

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treatment options available, the overall survival of patients with advanced stages seems to have improved.

Additional prognostic markers are available to predict the prognosis of patients with CLL, in particular at early stages. Patients with a detectable del(17p) (5%–10% of patients) have the poorest prognosis with a median overall survival time of 2–3 years. Another poor prognostic marker is the del(11q), which is found in ~20% of the patients. However, the poor outcome of patients with del(11q) is overcome by chemoimmunotherapy with fludarabine, cyclophosphamide, rituximab (FCR) (see below).

About 50% of CLL patients present with an unmutated IGHV status. These patients have a significantly shorter overall survival time and time to initiation of treatment. The expression of CD38, ZAP70 seems to correlate with the IGHV mutational status to some extent. In contrast to molecular cytogenetics (FISH), these analyses should not influence the treatment indication in CLL. Their value needs further investigation in clinical trials [III, C].

management of early disease

(Binet stage A and B without active disease; Rai 0, I and II without symptoms)

The standard treatment of patients with early disease is a watch-and-wait strategy. Blood cell counts and clinical examinations should be performed every 3–12 months [I, A]. In patients with active disease as defined below treatment may be initiated.

**treatment of advanced disease**

(Binet stage A and B with active disease, Binet stage C; Rai 0–II with symptoms, Rai III–IV)

The following conditions define active disease and may represent an indication for therapy: significant B symptoms, cytopenias not caused by autoimmune phenomena and symptoms or complications from lymphadenopathy, splenomegaly or hepatomegaly as well as autoimmune anaemia and/or thrombocytopenia poorly responsive to corticosteroid therapy [I, A].

The fitness and comorbidity of patients should be evaluated for the choice of the treatment. Improved survival has recently been demonstrated following first-line immunohemotherapy with FCR in physically fit patients with CLL [II, A].

Therefore in this patient group (physically active, no major health problems, normal renal function) FCR is now the standard first-line therapy.

In patients with relevant comorbidity chlorambucil [II, B] remains the standard therapy. Alternatives are dose-reduced purine analogue-based therapies (FC, PCR) [III, B] or bendamustine [II, B].

Patients showing a chromosomal defect del(17p) frequently do not respond to conventional chemotherapy with fludarabine or FC. Even after FCR therapy, progression free survival of these patients remains short. Therefore, these patients with sufficient fitness should be offered allogeneic stem cell transplantation within clinical trials [III, B].

**second-line chemotherapy**

The first-line treatment may be repeated, if the relapse or progression occurs at least 12 months after the initial therapy and 24 months after immunohemotherapy [III, B].

If the relapse occurs within 12 months after monotherapy or 24 months after immunohemotherapy, or if the disease does not respond to first-line monotherapy, the therapeutic regimen needs to be changed to one of the following options [III, B].

- Alemtuzumab-containing regimen followed by allogeneic stem cell transplantation in physically fit patients.
- FCR for patients relapsed or refractory to first-line therapy with an alkylating agent.
- Alemtuzumab- or bendamustine-containing regimen in physically non-fit patients without del(17p). In these patients an attempt with high-dose ofatumomab or rituximab with high-dose steroids can be made.
- Alemtuzumab in physically non-fit patients with del(17p).

In order to achieve better efficacy in patients with bulky disease alemtuzumab may be combined with fludarabine or steroids. Allogeneic stem cell transplantation is the only curative therapy and is indicated in high risk [del(17p), del(11q)] and/or refractory disease. Autologous HSCT does not seem to yield better results than immunomochemotherapies and should be abandoned [III, B].
About 10% (3%–16%) of the patients develop Richter’s syndrome with transformation into an aggressive lymphoma, Hodgkin’s lymphoma or prolymphocytic leukaemia (PLL). The prognosis of Richter’s syndrome as well as B-PLL is very poor. Polychemotherapies with antibodies are a treatment option, but do not result in long-lasting remission. Allogeneic stem cell transplantation is an experimental option, which may be considered in all physically fit patients with Richter’s Syndrome.

response evaluation

Response evaluation includes careful physical examination and a blood cell count. A marrow biopsy is recommended for the proper definition of complete remission, in particular in clinical trials [III, B]. Chest X-ray and an abdominal ultrasound or computerized tomography for response evaluation should be performed, if abnormal before therapy [IV, C].

Detection of minimal residual disease (MRD) by four-colour flow cytometry has prognostic impact on the duration of remission. Patients who have become MRD negative after the end of treatment have a significantly longer response duration. However, the clinical consequences of a MRD signal after the end of therapy are unclear. Therefore, the analysis of MRD should be performed in clinical trials, but not in general routine.

follow-up

Follow-up of asymptomatic patients should include a blood cell count, and the palpation of lymph nodes, liver and spleen every 3 months. Special attention should be paid to the appearance of autoimmune cytopenias (autoimmune haemolytic anaemia, autoimmune thrombocytopenia), which occur in 10%–15% of CLL patients.

Patients with CLL have a two- to sevenfold increase risk of developing secondary malignancies, including secondary MDS or AML as well as solid tumors.

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

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