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

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incidence and epidemiology

Chronic lymphocytic leukaemia (CLL) is the most common leukaemia in the Western world with an incidence of 4.2:100 000/year. The incidence increases to >30:100 000/year at an age of >80 years. The median age at diagnosis is 72 years. About 10% of the CLL patients are reported to be younger than 55 years. There is an inherited genetic susceptibility for CLL, with a 6- to 9-fold increased risk for family members of CLL patients.

diagnosis and molecular biology

The diagnosis of CLL is established by the following criteria [1]:
- Presence in the peripheral blood of ≥5000 monoclonal B lymphocytes/µl. 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-appearing lymphocytes with a narrow border of cytoplasm and a dense nucleus lacking discernible nucleoli, and having partially aggregated chromatin. Larger, atypical lymphocytes or prolymphocytes may be seen but must not exceed 55%.

CLL cells co-express the CD5 antigen 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 kappa or lambda immunoglobulin light chains.

Other lymphoma entities to be separated from CLL are leukemic marginal zone lymphoma, lymphoplasmacytic lymphoma and mantle cell lymphoma (MCL). These tumour cells express B-cell surface antigens and MCL also expresses CD5, but usually not CD23. For cases that express CD23, staining for cyclin D1 or SOX11 and fluorescence in situ hybridisation (FISH) for detecting a translocation (11;14) are useful for establishing the diagnosis of MCL. FMC7 may also help differentiating CLL from MCL, but there are also FMC7 positive (atypical) CLL cases. Marginal zone lymphoma or lymphoplasmacytic lymphoma may also be differentiated by a negative or lower CD43 expression in comparison to CLL.

In the World Health Organization classification, small lymphocytic lymphoma (SLL) and CLL are considered to be a single entity. The diagnosis of SLL requires the presence of lymphadenopathy and/or splenomegaly with a number of B lymphocytes in the peripheral blood not exceeding 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.

In absence of lymphadenopathy, organomegaly, cytopenia and clinical symptoms, the presence of fewer than 5000 monoclonal B lymphocytes/µl defines ‘monoclonal B-lymphocytosis’ (MBL) [1], which can be detected in 5% of subjects with normal blood count [2]. Progression to CLL occurs in 1%–2% of MBL cases per year [2].

staging and risk assessment

The following examinations are recommended before any treatment (Table 1) [III, B] [1]:
- History and physical examination including a careful palpation of all lymph node areas, spleen and liver
- Complete blood cell count and differential count
- Serum chemistry including lactate dehydrogenase, bilirubin, serum immunoglobulins, direct antiglobulin test
- The history and status of relevant infections [i.e. hepatitis B and C, cytomegalovirus, human immunodeficiency virus] should be evaluated before chemoimmunotherapy or allogeneic stem-cell transplantation (alloSCT), to avoid virus re-activation

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FISH for detection of deletion of the chromosome 17 [del (17p)] affecting the tumour protein p53 expression and in the absence of del(17p) molecular genetics for detection of TP53 gene mutation (at least exons 4–10, eventually exons 2–11) [III, A] [3].

The following additional examinations before treatment are desirable [III, B] [1]:

- Although a bone marrow biopsy is not required for diagnosis, it is recommended for the diagnostic evaluation of unclear cytopenias, or FISH or molecular genetics if peripheral blood cell lymphocytosis does not allow adequate immunophenotyping

- An extended FISH analysis is recommended before the start of therapy because the detection of additional cytogenetic abnormalities [del(11q) or trisomy 12] may have therapeutic consequences

- Molecular analysis for detecting immunoglobulin heavy chain variable (IGHV) mutation status and better estimation of duration of response

- Imaging studies by computed tomography (CT) scans may be helpful to assess the tumour load or to determine the cause of unclear symptoms in individual patients, but they should not generally be used in asymptomatic patients or for clinical staging. In addition, CT scans may be useful for baseline and final assessment in clinical trials [III, C]. In elderly patients, abdominal ultrasound might be considered instead.

Two clinical staging systems are used to predict median survival (Table 2) [4, 5]. In Europe, the Binet staging system is more widely used, whereas in the United States, the Rai system is more commonly applied. Both Binet and Rai staging systems separate three groups of patients with different prognoses (Table 2) [4, 5]. With the new treatment options available, the overall survival (OS) of patients with advanced disease stages has improved [6].

Additional markers are available to predict the prognosis of patients with CLL, in particular at early stages [7, 8]. Patients with a detectable del(17p) or a mutation of TP53 (∼5% at diagnosis and up to 10% at treatment initiation) have the poorest prognosis, with a median OS of 2–5 years. The formerly poor prognosis of patients with a del(11q) (∼20%) has been improved by chemoimmunotherapy with FCR (fludarabine, cyclophosphamide and rituximab) [9]. More recently described gene mutations such as NOTCH1, SF3B1, MYD88 or BIRC3 [10] may also predict an unfavourable prognosis in the absence of TP53 deletion/mutation [11, 12], but their clinical impact needs further investigation [III, C]. Because leukaemic clones may evolve, FISH and TP53 mutation analyses should be repeated before relapse treatment is administered [III, B] [13].

About 50% of CLL patients present with an unmutated IGHV status [14, 15]. CLL cells with unmutated IGVH status have a higher genetic instability with a higher risk of gaining unfavourable genetic mutations. OS and time to treatment intervention are significantly shorter in this patient group. The expression of CD38 and ZAP70 correlates to some extent with the IGHV mutational status, but has no therapeutic impact and is therefore not required [III, C].

### Table 1. Diagnostic and staging work-up

<table>
<thead>
<tr>
<th>Pretreatment evaluation</th>
<th>Response evaluation</th>
</tr>
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<tbody>
<tr>
<td>History, physical examination and performance status</td>
<td>+</td>
</tr>
<tr>
<td>Complete blood count and differential</td>
<td>+</td>
</tr>
<tr>
<td>Serum chemistry including serum immunoglobulin and direct antiglobulin test</td>
<td>+</td>
</tr>
<tr>
<td>Cytogenetics (FISH) for del (17p)/molecular genetics for TP53 mutation</td>
<td>+</td>
</tr>
<tr>
<td>Marrow aspirate and biopsy</td>
<td>+</td>
</tr>
<tr>
<td>Hepatitis B and C, CMV and HIV serology</td>
<td>+</td>
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</tbody>
</table>

*Only if clinically indicated. *Only for confirmation of CR within clinical studies.

FISH, fluorescence in situ hybridisation; CMV, cytomegalovirus; HIV, human immunodeficiency virus; CR, complete remission.

### Table 2. Staging systems for chronic lymphocytic leukaemia (CLL)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Definition</th>
<th>Median survival</th>
</tr>
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<tbody>
<tr>
<td>Binet system</td>
<td></td>
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<tr>
<td>Binet A</td>
<td>Hb ≥ 10.0 g/dl, thrombocytes ≥100 × 10^9/l, &lt;3 lymph node regions</td>
<td>&gt;10 years</td>
</tr>
<tr>
<td>Binet B</td>
<td>Hb ≥ 10.0 g/dl, thrombocytes ≥100 × 10^9/l, ≥3 lymph node regions</td>
<td>&gt;8 years</td>
</tr>
<tr>
<td>Binet C</td>
<td>Hb &lt; 10.0 g/dl, thrombocytes &lt;100 × 10^9/l</td>
<td>6.5 years</td>
</tr>
<tr>
<td>Rai system</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rai 0</td>
<td>Lymphocytosis &gt;15 × 10^9/l</td>
<td>&gt;10 years</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rai I</td>
<td>Lymphocytosis and lymphadenopathy</td>
<td>&gt;8 years</td>
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<tr>
<td>Rai II</td>
<td>Lymphocytosis and hepatomegaly and/or splenomegaly with/without lymphadenopathy</td>
<td></td>
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<tr>
<td>High risk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rai III</td>
<td>Lymphocytosis and Hb &lt; 11.0 g/dl with/without lymphadenopathy/organomegaly</td>
<td>6.5 years</td>
</tr>
<tr>
<td>Rai IV</td>
<td>Lymphocytosis and thrombocytes &lt;100 × 10^9/l with/without lymphadenopathy/organomegaly</td>
<td></td>
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</table>

The overall survival times included in this table were adapted and have changed during the past 30 years [7]. Binet’s lymphoid areas consist in: lymphadenopathy either uni- or bilateral in (1) cervical, (2) axillary, (3) inguinal areas, (4) spleen, (5) liver. Hb, haemoglobin.
management of early disease stage

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

Previous studies have shown that early treatment with chemotherapeutic agents does not translate into a survival advantage in patients with early-stage CLL [16]. The standard treatment of patients with early disease is a watch-and-wait strategy [I, A]. Blood cell counts and clinical examinations should be carried out every 3–12 months.

Due to the lack of clinical trials, no evidence-based treatment recommendation can be given for localised, early-stage SLL [I, A].

treatment of advanced disease stage

Binet stage A and B with active disease or Binet stage C; Rai 0–II with active disease or Rai III–IV treatment indication.

Treatment should only be initiated in patients with symptomatic, active disease. The following conditions define active disease: significant B symptoms, cytopenias not caused by autoimmune phenomena and symptoms or complications from lymphadenopathy, splenomegaly or hepatomegaly, lymphocyte doubling time of <6 months (only in patients with more than 30G lymphocytes/l), as well as autoimmune anaemia and/or thrombocytopenia poorly responsive to conventional therapy [I, A]. The presence of del(17p) or TP53 mutation without the above-mentioned conditions is not an indication for treatment.

front-line treatment. In physically fit patients (physically active, with no major health problems, normal renal function) without TP53 deletion/mutation, FCR is the standard first-line therapy: improvement of OS has been demonstrated with this first-line chemoimmunotherapy (Figure 1) [I, A] [9]. Combinations based on other purine analogues such as cladribine [17] or pentostatin [18] have shown similar activity, but it is uncertain whether they can replace fludarabine in the FCR regimen [II, B]. In fit but elderly patients, FCR was shown to be associated with a higher rate of severe infections when compared with bendamustine plus rituximab (BR) [19]. Therefore, in this group of patients, therapy with BR may be considered, although it produces fewer complete remissions than FCR [I, B]. Further studies evaluating BR as front-line therapy in fit but elderly patients are therefore required.

In patients with relevant co-morbidity, who are usually older, but without TP53 deletion/mutation, the combination of chlorambucil plus an anti-CD20 antibody (rituximab, ofatumumab or obinutuzumab) prolongs progression-free survival (PFS) when compared with monotherapy and is therefore the standard approach [I, A] [20, 21]. In a head-to-head comparison of chlorambucil-based combinations, the type II antibody obinutuzumab was superior to the type I antibody rituximab with regard to PFS, complete remission (CR) and minimal residual disease (MRD)-negative remissions.

Figure 1. Front-line treatment. CLL, chronic lymphocytic leukaemia; SLL, small lymphocytic leukaemia; BCR, B-cell receptor; R, rituximab; alloHSCT, allogeneic haematopoietic stem cell transplantation; FCR, fludarabine, cyclophosphamide and rituximab; BR, bendamustine plus rituximab; Clb, chlorambucil.
Patients with TP53 deletion/mutation have a poor prognosis even after FCR therapy [9]. Therefore, it is recommended that patients with TP53 deletion/mutation are treated with novel inhibitors (ibrutinib; idelalisib and rituximab) in front-line and relapse settings [V, A]. For fit patients responding to inhibitor treatment, an allogeneic haematopoietic stem-cell transplantation (HSCT) may be discussed, using individual and transplant-related risk factors [III, B] [22].

Maintenance therapy in CLL patients with higher risk of relapse may have some benefit, but cannot be generally recommended.

treatment of relapse and refractory disease. As for the first-line therapy, treatment at relapse should only be started in symptomatic patients. Many patients with relapsed but asymptomatic CLL can be followed with no therapy for a long period of time.

First-line treatment may be repeated if the relapse or progression occurs at least 24–36 months after chemoimmunotherapy and if TP53 deletion/mutation was excluded [III, B].

If relapse occurs within 24–36 months after chemoimmunotherapy, or if the disease does not respond to any first-line therapy, the therapeutic regimen should be changed.

Treatment options include [III, B]:

- BCL2 antagonists alone or in combination within a clinical study
- Bruton’s tyrosine kinase inhibitor ibrutinib [23]
- PI3K inhibitor idelalisib in combination with rituximab [24]
- Other chemoimmunotherapy combinations should only be administered if TP53 deletion/mutation was excluded (Figure 2).

Patients not responding nor progressing upon therapy with kinase inhibitors might be switched to a different kinase inhibitor or to BCL2 antagonists when available (according to clinical trials). Fit patients achieving second remission following the second application of an inhibitor should proceed to allogeneic HSCT [V, B] [22].

the role of haematopoietic stem-cell transplantation. Autologous stem-cell transplantation is not useful in CLL [I, A] [25]. An alloSCT should be considered in patients achieving remission with kinase inhibitors or BCL2 antagonists after early relapse from chemoimmunotherapy and/or with del(17p) or TP53 mutation. In this situation, long-term treatment with inhibitors is an alternative option. The decision should be based on

Figure 2. Relapse treatment. CLL, chronic lymphocytic leukaemia; SLL, small lymphocytic leukaemia; BCR, B-cell receptor; R, rituximab; BR, bendamustine plus rituximab; FCR, fludarabine, cyclophosphamide and rituximab; alloHSCT, allogeneic haematopoietic stem cell transplantation.
treatment of CLL complications. Treatment of patients with autoimmune cytopaenia should be carried out according to the statement from the ESMO guidelines consensus conference on malignant lymphoma: CLL [26]. Most patients with autoimmune cytopaenia respond to corticosteroids [III, B]. For patients not responding to corticosteroids, rituximab administration might be a reasonable treatment option before splenectomy [III, B]. In patients with resistant autoimmune cytopaenia, treatment of the underlying CLL is recommended.

Infections are a common complication in CLL patients; therefore, use of immunosuppressive agents, as for example corticosteroids, should be restricted to a possible minimum. The use of prophylactic systemic immunoglobulin does not have an impact on OS [27, 28], and is only recommended in patients with severe hypogammaglobulinaemia and repeated infections [I, A]. Antibiotic and antiviral prophylaxis should be used in patients with recurrent infections and/or very high risk of developing infections (e.g. pneumocystis prophylaxis during treatment with chemoimmunotherapies based on purine analogues or bendamustine) [IV, B]. Pneumococcal vaccination as well as seasonal influenza vaccination is recommended in early-stage CLL [IV, B].

Response evaluation. Response evaluation includes a careful physical examination and a blood cell count. A bone marrow biopsy may be carried out to define CR [III, B] [1]. Chest X-ray and an abdominal ultrasound or CT for response evaluation may be carried out, if abnormal before therapy [IV, C] [1].

Detection of MRD by four-colour flow cytometry has a strong prognostic impact [29, 30]. Patients who are MRD-negative after therapy show a longer response duration and survival. Additional clinical consequences of MRD positivity post-therapy remain unclear except for patients after an allogeneic transplantation, where a positive MRD signal may trigger the reduction of immunosuppressive therapies or the start of anti-leukaemic maintenance therapy. Therefore, MRD assessment is not generally recommended for monitoring post-therapy outside clinical studies.

personalised medicine

Principles of personalised or precision medicine in CLL have remained somewhat elusive. There is ample evidence that the comprehensive evaluation of prognostic factors in early-stage CLL improves the prediction of the individual prognosis [7]. However, a complete prognostic work-up often has no clinical consequences. Therefore, the initial assessment of a CLL patient can be carried out with a limited set of parameters (see above).

In contrast, a complete genetic work-up should be carried out when CLL becomes symptomatic and requires treatment. In this situation, genetic aberrations such as TP53 mutations alter the choice of therapy (see above). Moreover, fitness and comorbidities of the patient (as assessed e.g. by using the cumulative illness rating scale [31]) may influence the choice of therapy.

follow-up and long-term implications

CLL is an incurable disease. Therefore, life-long observation and follow-up is recommended for all patients. Follow-up of asymptomatic patients should include a blood cell count and the palpation of lymph nodes, liver and spleen every 3–12 months depending on the dynamics of the leukaemic development. Special attention should be paid to the appearance of autoimmune cytopaenias. Moreover, CLL patients have a two- to sevenfold increased risk of developing secondary malignancies (mostly solid cancers, but also secondary myelodysplastic syndromes or acute myeloblastic leukaemia).

The transformation into a diffuse large B-cell lymphoma (DLBCL) or Hodgkin’s lymphoma (HL) occurs in 2%–15% of CLL patients during the course of their disease. The diagnosis has to be confirmed by histopathology exam of a lymph node (biopsy or excision). A positron emission tomography–CT might be useful to guide biopsy [IV, C]. The transformation of CLL into Hodgkin’s disease represents a separate entity, where conventional chemotherapy against HL often achieves long-lasting remissions. The transformation into DLBCL is called Richter’s transformation (RT) and usually has a very poor prognosis, with the exception of clonally-unrelated de novo DLBCL. Treatment regimens for RT include therapies used in DLBCL such as rituximab plus CHOP (cyclophosphamide, vincristine, doxorubicin and dexamethasone). More intense treatment regimens such as rituximab plus hyper CVAD (cyclophosphamide, vincristine, doxorubicin and dexamethasone alternating with methotrexate and cytarabine) or OFAR (oxaliplatin, fludarabine, cytarabine and rituximab) have not been proven to induce better outcomes than R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone) [IV, B]. Response duration of RT is typically short, and an allogeneic HSCT should be recommended to all patients with clonally related DLBCL with an available donor and sufficient fitness [IV, B].

methodology

These clinical practice guidelines were developed in accordance with the ESMO standard operating procedures for clinical practice guidelines development. The relevant literature has been selected by the expert authors. Levels of evidence and grades of recommendation have been applied using the system shown in Table 3. Statements without grading were considered justified standard clinical practice by the experts and the ESMO faculty. This manuscript has been subjected to an anonymous peer review process.

conflict of interest

BE has reported honoraria from Celgene, Gilead, GlaxoSmithKline, Janssen, Mundipharma and Roche and has received research grants from Mundipharma and Roche. TR has reported honoraria from Roche and Janssen and research grants from Roche, Janssen, GlaxoSmithKline, Pharmacycics and Gilead. EM has reported honoraria from Janssen, Pharmacycics and Pfizer. PG has reported honoraria from Abbvie, Gilead,
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