

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

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### incidence

Chronic lymphocytic leukemia (CLL) is the most common leukemia in the Western world with an incidence of 4.2/100 000/year [1]. 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 CLL patients are reported to be younger than 55 years.

### diagnosis

The diagnosis of CLL is established by the following criteria [2]:

- The presence in the peripheral blood of  $\geq 5000$  monoclonal B lymphocytes/ $\mu\text{l}$  for the duration of at least 3 months. The clonality of the circulating B lymphocytes needs to be confirmed by flow cytometry.
- The leukemia cells found in the blood smear are characteristically small, mature lymphocytes with a narrow border of cytoplasm and a dense nucleus lacking discernible nucleoli and having partially aggregated chromatin.

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 leukemia cells is restricted to expression of either  $\kappa$  or  $\lambda$  immunoglobulin light chains.

In contrast, the leukemia cells of mantle cell lymphoma, despite also expressing B-cell surface antigens and CD5, generally do not express CD23. For cases which express CD23, cyclin D1 staining or fluorescence *in situ* hybridization (FISH) for detecting a translocation (11;14) are useful to diagnose

mantle cell lymphoma in leukemic phase. Other lymphoma entities to be separated from CLL are marginal zone lymphoma and immunocytoma.

In the World Health Organization (WHO) classification, small lymphocytic lymphoma (SLL) and CLL are considered to be the same entity. The diagnosis of SLL requires the presence of lymphadenopathy and/or splenomegaly, with the number of B lymphocytes in the peripheral blood not exceeding  $5 \times 10^9/\text{l}$ . SLL cells show the same immunophenotype as CLL cells. The diagnosis of SLL should be confirmed by histopathological evaluation of a lymph node biopsy whenever possible.

In the absence of lymphadenopathy and organomegaly, cytopenias and clinical symptoms, the presence of  $< 5000$  monoclonal B lymphocytes/ $\mu\text{l}$  is defined as 'monoclonal B-lymphocytosis' (MBL) [2]. Progress to CLL occurs in 1–2% of MBL cases per year [3].

The following examinations are recommended prior to treatment initiation [III, B] [2]:

- 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 (LDH), bilirubin, serum immunoglobulin, direct antiglobulin test (DAT).
- The status of relevant infections [hepatitis B and C, cytomegalovirus (CMV), human immunodeficiency virus (HIV)] should be evaluated prior to chemoimmunotherapy, alemtuzumab or allogeneic stem cell transplantation to avoid virus (re-)activation.

The following additional examinations prior to treatment are desirable [III, B] [2]:

- Although a bone marrow biopsy is not required for diagnosis, it is strongly recommended prior to initiating myelosuppressive therapies and for the diagnostic evaluation of unclear cytopenias.
- The detection of cytogenetic abnormalities, in particular of a deletion of chromosome 17 [del(17p)] and 11 [del(11q)] by FISH may have therapeutic consequences. Therefore, a FISH analysis is recommended prior to the start of therapy.
- Computed tomography (CT) scans are recommended for baseline and final assessment in clinical trials [III, C], but not as a routine practice outside of clinical trials. Clinical staging should not be based on imaging studies.

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Approved by the ESMO Guidelines Working Group: August 2003, last update July 2011. This publication supersedes the previously published version—Ann Oncol 2010; 21 (Suppl 5): v162–v164.

Conflict of interest: Dr Eichhorst has reported that she is conducting research sponsored by Mundipharma and Roche and that she is a member of the speakers' bureau for Roche; Professor Hallek has reported that he has received research grants from Roche and Mundipharma and that he is a speaker for Roche and Mundipharma; Professor Dreyling has reported that he has received support for research from Roche and that he is a member of its advisory board. Dr Robak and Dr Montserrat have reported no conflicts of interest.

## staging and risk assessment

The median survival from diagnosis varies between 18 months and >10 years. Two clinical staging systems are used [4, 5]. In Europe, the Binet staging system is the more widely used. These staging systems separate three groups of different prognosis (Table 1) [4, 5]. With the new treatment options available, the overall survival of patients with advanced stages has improved [6].

Additional prognostic markers are available to predict the prognosis of patients with CLL, in particular at early stages [7]. Patients with a detectable del(17p) or a mutation of the p53 gene (5–10% of the patients) have the poorest prognosis, with a median overall survival of 2–3 years. Another poor prognostic marker has been del(11q), which is found in ~20% of the patients. However, the poor outcome of patients with del(11q) is overcome by chemoimmunotherapy with FCR (fludarabine, cyclophosphamide and rituximab) [8].

About 50% of CLL patients present with an unmutated IGHV (immunoglobulin heavy chain variable) status [9, 10]. These patients have a significantly shorter overall survival time and shorter time to treatment intervention. The expression of CD38, ZAP70 seems to correlate with the IGHV mutational status to some extent [11]. The prognostic value of these markers needs further assessment in prospective clinical trials, but, in contrast to molecular cytogenetics (FISH), they do not influence treatment modality [III, C].

## treatment indications

Treatment should only be given to patients with active, symptomatic 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 >30 000 lymphocytes/ $\mu$ l) as well as autoimmune anemia and/or thrombocytopenia poorly responsive to conventional therapy [I, A].

## treatment by disease stage

### treatment of early, stable disease

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

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

### treatment of advanced, active disease

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

The fitness and co-morbidity of patients need to be evaluated for the choice of the treatment. For assessing the co-morbidity burden, the cumulative illness rating scale represents a helpful tool [13].

An improved survival has been demonstrated following first-line chemoimmunotherapy with FCR in physically fit patients with CLL [I, A] [8]. Therefore, in this patient group (physically active, no major health problems, normal renal function) FCR is the standard first-line therapy. Combinations based on other purine analogs such as cladribine [14] or pentostatin [15] have shown similar activity, but it is uncertain whether they can replace fludarabine in the FCR regimen [II, B].

**Table 1.** Staging systems for CLL

Stage	Definition	Median survival
<b>Binet system</b>		
Binet A	Hb $\geq$ 10.0 g/dl, platelets $\geq$ 100 $\times$ 10 <sup>9</sup> /l, <3 lymph node regions	>10 years
Binet B	Hb $\geq$ 10.0 g/dl, platelets $\geq$ 100 $\times$ 10 <sup>9</sup> /l, $\geq$ 3 lymph node regions	>8 years
Binet C	Hb <10.0 g/dl, platelets <100 $\times$ 10 <sup>9</sup> /l	6.5 years
<b>Rai system</b>		
Low risk		
Rai 0	Lymphocytosis $>$ 15 $\times$ 10 <sup>9</sup> /l	>10 years
Intermediate risk		
Rai I	Lymphocytosis and lymphadenopathy	>8 years
Rai II	Lymphocytosis and hepatomegaly and/or splenomegaly with/without lymphadenopathy	
High risk		
Rai III	Lymphocytosis and Hb <11.0 g/dl with/without lymphadenopathy/organomegaly	6.5 years
Rai IV	Lymphocytosis and platelets <100 $\times$ 10 <sup>9</sup> /l with/without lymphadenopathy/organomegaly	

The overall survival times included in this table are adapted to recently published data [29]. Hb, hemoglobin.

In patients with relevant co-morbidity, chlorambucil [II, B] seems to be the standard therapy [16]. Alternatives are dose-reduced purine analog-based therapies [FC, PCR (pentostatin, cyclophosphamide and rituximab) [III, B] or bendamustine [II, B] [17].

Patients showing a chromosomal defect del(17p) or p53 mutation frequently do not respond to conventional chemotherapy with fludarabine or FC. Even after FCR therapy, progression-free survival of these patients remains short [8]. Therefore, physically fit (and young) patients should be offered an effective initial regimen, of which alemtuzumab is currently

the most widely explored, followed by an allogeneic stem cell transplantation within clinical trials [III, B] [18, 19].

### treatment of relapse and refractory disease

The first-line treatment may be repeated, if the relapse or progression occurs at least 12–24 months after a monotherapy or 24–36 months after chemoimmunotherapy, respectively [III, B].

If relapse occurs within 12–24 months after monotherapy or 24–36 months after chemoimmunotherapy, or if the disease does not respond to any first-line therapy, the therapeutic regimen needs to be changed to one of the following options [III, B]:

- Salvage regimen, e.g. alemtuzumab, followed by allogeneic stem cell transplantation in physically fit patients [18].
- FCR for patients relapsed or refractory to first-line therapy with an alkylating agent [20].
- A bendamustine- or alemtuzumab-containing regimen in physically non-fit patients without del(17p) [21]. In subsequent relapses, an attempt with high-dose ofatumumab or rituximab with high-dose steroids can also be made [6, 22].
- An alemtuzumab-containing regimen in patients with del(17p).

In order to achieve better efficacy in patients with bulky disease, alemtuzumab may be combined with fludarabine or steroids [23].

Allogeneic stem cell transplantation is the only curative therapy and is especially indicated in very high risk [del(17p), p53 mutation] and/or refractory disease [18]. The use of autologous hematopoietic stem cell transplantation does not seem to yield better results than chemoimmunotherapies [III, B].

**Table 2.** Diagnostic and staging work-up

	Pretreatment evaluation	Staging
History, physical examination and performance status	+	+
Complete blood count and differential	+	+
Serum chemistry including serum immunoglobulin and direct antiglobulin test	+	+
Cytogenetics (FISH) for del(17p)	+	–
Marrow aspirate and biopsy	+ <sup>a</sup>	+ <sup>b</sup>
Hepatitis B and C, CMV and HIV serology	+	–

<sup>a</sup>Only if clinically indicated.

<sup>b</sup>Only for confirmation of complete response.

CMV, cytomegalovirus; FISH, fluorescence *in situ* hybridization; HIV, human immunodeficiency virus.

**Table 3.** Management by stage, risk categories and physical fitness

Stage	Fitness	Molecular cytogenetics	First-line therapy
Asymptomatic Binet A–B or Rai 0–II	Irrelevant	Irrelevant	None
Binet C or Rai III–IV, or symptomatic disease (any stage)	Go Go	No del(17p)	FCR
	Slow Go	del(17p)	FCR, A or FA → Allo SCT CLB A
<b>Relapse</b>	<b>Fitness</b>	<b>Molecular cytogenetics</b>	<b>Relapse therapy</b>
Early (<12–24 months after monotherapy or <24–36 months after chemoimmunotherapy)	Go Go	No del(17p)	After chemoimmunotherapy: BR, A or FA → Allo SCT After monotherapy: FCR A or FA → Allo SCT
	Slow Go	del(17p) No del(17p) del(17p)	FCR <sup>a</sup> , B, A, O, R + HDS A
Late (>12–24 months after monotherapy or >24–36 months after chemoimmunotherapy)	Go Go and Slow Go		Repeat first line

<sup>a</sup>Not recommended for patients refractory to fludarabine.

‘Go go’ defines patients with a good physical fitness and low co-morbidity burden, ‘Slow Go’ defines patients with impaired physical fitness and relevant comorbidity burden).

A, alemtuzumab; Allo SCT, allogeneic stem cell transplantation; B, bendamustine; C, cyclophosphamide; CLB, chlorambucil; F, fludarabine; HDS, high-dose steroids; O, ofatumumab; R, rituximab.

There is no proven efficacy of consolidation or maintenance therapy in CLL. This strategy cannot be recommended outside clinical trials.

## treatment of CLL complications

Autoimmune cytopenia, especially autoimmune hemolytic anemia (AIHA), appears in 5–10% of CLL patients. In these patients, the prognosis is not as poor as in those cases in which the cytopenia is due to a massive bone marrow infiltration by the disease [24]. Most patients with autoimmune cytopenia respond to corticosteroids [III, B]. For patients not responding to corticosteroids, splenectomy is a reasonable treatment choice. Monoclonal antibodies and thrombopoietin analogs can be used [III, B] in selected cases not responding to corticosteroids and before splenectomy. In patients with resistant immune cytopenia, treatment of the underlying CLL is recommended.

Because most CLL patients develop a severe immune defect during the course of the disease, infections are a common complication. The use of prophylactic intravenous immunoglobulin does not have an impact on overall survival [25] and is therefore not recommended to be used as routine [II, B]. Antibiotic, antiviral or antifungal prophylaxis might be used in selected patients with recurrent infections and/or very high risk of developing infections (e.g. treatment with alemtuzumab, allogeneic stem cell transplantation) [IV, B]. The development of transformation into an aggressive lymphoma or Hodgkin's lymphoma (HD), a Richter's syndrome or B-cell prolymphocytic leukemia (B-PLL) occurs in 2–15% of CLL patients during the course of their disease. The diagnosis has to be confirmed by lymph node excision. The transformation of CLL into HD represents a separate entity, since conventional chemotherapy against HD often achieves long-lasting remissions. Otherwise, the prognosis of Richter's syndrome and B-PLL is very poor. A rituximab-containing regimen, for example rituximab plus hyper CVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone alternating with methotrexate and cytarabine) or OFAR (oxaliplatin, fludarabine, cytarabine and rituximab) for Richter's syndrome and FCR for B-PLL, is recommended for remission induction [IV, B]. Because of the short response duration of Richter's syndrome, an allogeneic stem cell transplantation should be considered in patients with available donors and sufficient fitness [IV, D].

## response evaluation

Response evaluation includes careful physical examination and a blood cell count. A marrow biopsy is recommended for the proper definition of complete remissions, in particular in clinical trials [III, B] [2]. Chest X-ray and an abdominal ultrasound or CT for response evaluation can be performed, if abnormal prior to therapy [IV, C] [2].

Detection of minimal residual disease (MRD) by four-color flow cytometry has prognostic impact [26]. Patients who have become MRD negative after the end of treatment have a significantly longer response duration and also a longer

survival. However, the clinical consequences of an MRD signal after the end of therapy are unclear. Therefore, the analysis of MRD should be performed in clinical trials, but not as a general routine.

## prognosis

A large monocentric study has shown that the prognosis of CLL patients has improved during the past 30 years independently of stage of the disease [27]. The improved survival was mainly due to a decrease in CLL-attributable mortality in patients younger than 70 years and in patients with Binet stage B or C at diagnosis [III, B]. Moreover, chemoimmunotherapy combinations have been shown to prolong the overall survival in physically fit patients with advanced stage disease [I, A] [8, 28]. In spite of these combinations, patients with del(17p) as well as primary refractory patients still have an impaired prognosis with a median overall survival of <36 months [II, A]. Due to the lack of appropriate therapeutic interventions, the prognosis of early stage CLL has remained unchanged and is dependent on the individual risk profile [I, A].

## follow-up

Follow-up of asymptomatic patients should include a blood cell count, and the palpation of lymph nodes, liver and spleen every 3–12 months. Special attention should be paid to the appearance of autoimmune cytopenias as well as the development of a Richter's syndrome or prolymphocytic leukemia. Moreover, patients with CLL have a 2- to 7-fold increased risk of developing secondary malignancies, including secondary myelodysplastic syndromes or acute myelogenous leukemia as well as solid tumors.

## acknowledgements

Thanks are due to Federico Caligaris-Cappio, Peter Dreger, Christian Geisler, John Gribben, Eva Kimby and Stephan Stilgenbauer for helpful comments and suggestions, to Claire Bramley for her assistance, and to the European Research Initiative on CLL (ERIC) for its support.

## note

Levels of Evidence [IV] and Grades of Recommendation [AD] 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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